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FILE LAST UPDATED: 27 Aug 2002 (20020827/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d all hitstr tot l109

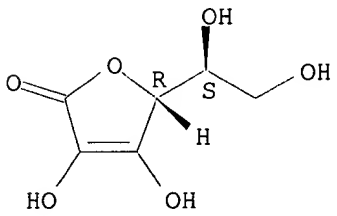
L109 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS
AN **2002:174956** HCAPLUS
DN **136:189309**
TI Blood substitute for oxygen transport and a method of preparing polymeric **hemoglobin**
IN Kuznetsova, N. P.; Gudkin, L. R.; Selivanov, E. A.; Bystrova, I. M.; Khanevich, M. D.; Mishaeva, R. N.; Panarin, E. F.; Gerbut, K. A.; Kochetygov, N. I.; Goncharov, A. V.; Molokovskaya, I. E.; Belov, E. V.
PA Rossiiskii Nauchno-Issledovatel'skii Institut Gematologii i Transfuziologii, Russia; Institut Vysokomolekulyarnykh Soedinenii RAN
SO Russ., No pp. given
CODEN: RUXXE7
DT Patent
LA Russian
IC ICM A61K038-42
ICS A61K009-08; A61K009-19
CC **63-3** (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
RU 2162707	C2	20010210	RU 1999-106110	19990324

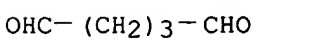
AB The invention relates to a blood substitute as oxygen transporter that is an aq. soln. contg. the following components, wt.%: polymeric **Hb**, 0.9-1.1; sodium chloride, 1.0-1.2; glucose, 0.68-0.83; **ascorbic acid**, 0.023-0.027; and water up to 100. The invention relates also to a compn. for prepg. a blood substitute as oxygen transporter contg., g per single therapeutic dose (400 mL of soln.): polymeric **Hb**, 3.6-4.4; sodium chloride, 0.7-0.9; glucose, 2.7-3.3; **ascorbic acid**, 0.9-0.11. Polymeric **Hb** is prepd. by interaction of deoxy-**Hb** with glutaraldehyde modified at pH 6.4-6.6 and 4-6 .degree.C with a dicarboxylic amino acid and sodium bisulfite.
ST blood substitute polymeric **Hb**

IT Blood substitutes
(blood substitute for oxygen transport and a method of prepg. polymeric **Hb**)
IT **Hemoglobins**
RL: BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(blood substitute for oxygen transport and a method of prepg. polymeric **Hb**)
IT **Hemoglobins**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(condensation products with glutaraldehyde; blood substitute for oxygen transport and a method of prepg. polymeric **Hb**)
IT **50-81-7, Ascorbic acid,** biological studies
50-99-7, Glucose, biological studies 7647-14-5, Sodium chloride, biological studies
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(blood substitute for oxygen transport and a method of prepg. polymeric **Hb**)
IT **111-30-8,** Glutaraldehyde
RL: RCT (Reactant); RACT (Reactant or reagent)
(blood substitute for oxygen transport and a method of prepg. polymeric **Hb**)
IT **50-81-7, Ascorbic acid,** biological studies
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(blood substitute for oxygen transport and a method of prepg. polymeric **Hb**)
RN 50-81-7 HCAPLUS
CN L-Ascorbic acid (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **111-30-8,** Glutaraldehyde
RL: RCT (Reactant); RACT (Reactant or reagent)
(blood substitute for oxygen transport and a method of prepg. polymeric **Hb**)
RN 111-30-8 HCAPLUS
CN Pentanedial (9CI) (CA INDEX NAME)



L109 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2002 ACS
AN **2000:688120** HCAPLUS
DN **133:271616**
TI **Hemoglobin-antioxidant conjugates**
IN **Adamson, James Gordon; McIntosh, Greg Angus**
PA **Hemosol Inc., Can.**
SO PCT Int. Appl., 49 pp.

CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K047-48
CC **63-3** (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000056367	A1	20000928	WO 2000-CA299	20000320

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1163010	A1	20011219	EP 2000-910473	20000320

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRAI CA 1999-2266174 A 19990318
WO 2000-CA299 W 20000320
OS MARPAT 133:271616
AB There are provided biocompatible chem. compns. having oxygen transporting capability and comprising oxygen transporting mols. chem. bound to **antioxidants**, to form compns. capable of protecting a mammalian body from oxidative damage. An example of a compn. according to the invention is **Hb** covalently coupled to a 6-hydroxy chroman carboxylic acid, such as **trolox**. **Trolox** was **conjugated** to carbonmonoxy-**Hb**, at a ratio of 1:1, using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride as a coupling agent. **Antioxidant** activity of the **conjugate** was studied in erythrocytes hemolysis mediated by peroxyl radicals.
ST **Hb antioxidant conjugate** prepn
IT Crosslinking agents
(Hb-antioxidant conjugates)
IT Polysaccharides, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(Hb-antioxidant conjugates)
IT Biopolymers
Polyoxyalkylenes, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates with Hb-antioxidant; Hb-antioxidant conjugates)
IT **Antioxidants**
(conjugates with Hb; Hb-antioxidant conjugates)
IT **Alkaloids, biological studies**
Carotenes, biological studies
Flavonoids
Isoflavonoids
Phenols, biological studies
Porphyrins
Quinones
Retinoids
Steroids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates with Hb; Hb-

antioxidant conjugates)

IT **Hemoproteins**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with **antioxidants**; **Hb-antioxidant conjugates**)

IT **Hemoglobins**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**, with **antioxidants**; **Hb-antioxidant conjugates**)

IT Hydroxamic acids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(di-tert-butylhydroxyphenylthio derivs, **conjugates** with **Hb**; **Hb-antioxidant conjugates**)

IT Ethers, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(phenolic, **conjugates** with **Hb**; **Hb-antioxidant conjugates**)

IT Polyamides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(poly(amino acids), **conjugates** with **Hb-antioxidant**; **Hb-antioxidant conjugates**)

IT Aldehydes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(polyfunctional; **Hb-antioxidant conjugates**)

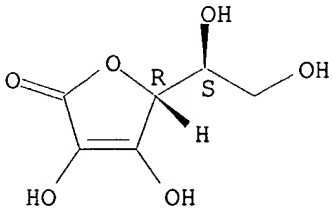
IT **50-81-7DP**, **Ascorbic acid**, derivs., **conjugates** with **Hb** **120-72-9DP**, **Indole**, amine derivs., **conjugates** with **Hb** **120-72-9DP**, **Indole**, **conjugates** with **Hb** **120-73-0DP**, **Purine**, analogs, **conjugates** with **Hb** **120-73-0DP**, **Purine**, analogs., **conjugates** with **Hb** **120-80-9P**, Catechol, biological studies **149-91-7DP**, Gallic acid, derivs., **conjugates** with **Hb** 487-26-3DP, Flavanone, **conjugates** with **Hb** **25322-68-3DP**, Polyethylene glycol, **conjugates** with **Hb-antioxidant** 27215-73-2DP, Flavanol, dihydro derivs., **conjugates** with **Hb** **36118-45-3DP**, **Pyrazoline**, derivs., **conjugates** with **Hb** **41903-66-6DP**, Chromanol, derivs., **conjugates** with **Hb** **53188-07-1DP**, **Trolox**, **conjugates** with **Hb** **56631-56-2DP**, derivs., **conjugates** with **Hb**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**Hb-antioxidant conjugates**)

IT **111-30-8**, Glutaraldehyde **151-51-9**, Carbodiimide **512-69-6**, **Raffinose** **578-19-8**, Diaspirin **1892-57-5** **53188-07-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**Hb-antioxidant conjugates**)

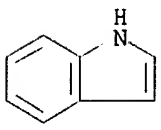
IT 7782-44-7, Oxygen, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transporign system for; **Hb-antioxidant conjugates**)
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Chen; DATABASE CHEMABS HCAPLUS
(2) Chen; FREE RADICAL BIOL MED 1994, V16(4), P437 HCAPLUS
(3) Hemosol Inc; WO 9956723 A 1999 HCAPLUS
(4) Hsia, J; BIOMATERIALS, ARTIFICIAL CELLS, AND IMMOBILIZATION BIOTECHNOLOGY 1992, V20/2-4, P587
(5) Hsia, J; DATABASE EMBASE
(6) Hunt, C; US 4425334 A 1984 HCAPLUS
(7) Kluger, R; WO 9700236 A 1997 HCAPLUS
(8) Mickle, D; US 5099012 A 1992 HCAPLUS
(9) Mordente, A; CHEMICAL RESEARCH IN TOXICOLOGY 1998, V11/1, P54
(10) Mordente, A; DATABASE EMBASE
(11) Pliura, D; US 5532352 A 1996 HCAPLUS
IT **50-81-7DP, Ascorbic acid**, derivs., **conjugates** with **Hb 120-72-9DP, Indole**, amine derivs., **conjugates** with **Hb 120-73-0DP, Purine**, analogs, **conjugates** with **Hb 120-80-9P**, Catechol, biological studies **149-91-7DP**, Gallic acid, derivs., **conjugates** with **Hb 25322-68-3DP**, Polyethylene glycol, **conjugates** with **Hb-antioxidant 36118-45-3DP**, **Pyrazoline**, derivs., **conjugates** with **Hb 41903-66-6DP**, Chromanol, derivs., **conjugates** with **Hb 53188-07-1DP, Trolox, conjugates** with **Hb 56631-56-2DP**, derivs., **conjugates** with **Hb**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**Hb-antioxidant conjugates**)
RN 50-81-7 HCAPLUS
CN L-Ascorbic acid (8CI, 9CI) (CA INDEX NAME)

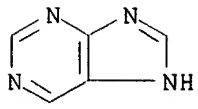
Absolute stereochemistry.



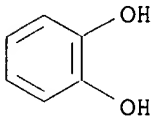
RN 120-72-9 HCAPLUS
CN 1H-Indole (9CI) (CA INDEX NAME)



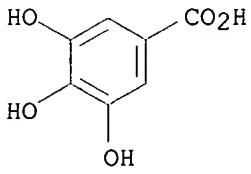
RN 120-73-0 HCAPLUS
CN 1H-Purine (9CI) (CA INDEX NAME)



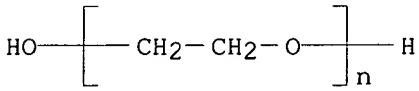
RN 120-80-9 HCAPLUS
CN 1,2-Benzenediol (9CI) (CA INDEX NAME)



RN 149-91-7 HCAPLUS
CN Benzoic acid, 3,4,5-trihydroxy- (9CI) (CA INDEX NAME)



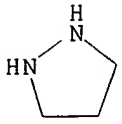
RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy- (9CI) (CA INDEX NAME)



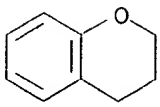
RN 36118-45-3 HCAPLUS
CN Pyrazole, dihydro- (9CI) (CA INDEX NAME)

CM 1

CRN 504-70-1
CMF C3 H8 N2

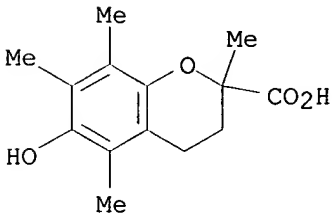


RN 41903-66-6 HCAPLUS
CN 2H-1-Benzopyranol, 3,4-dihydro- (9CI) (CA INDEX NAME)

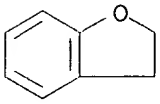


D1—OH

RN 53188-07-1 HCAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



RN 56631-56-2 HCAPLUS
CN Benzofuranol, 2,3-dihydro- (9CI) (CA INDEX NAME)



D1—OH

IT **111-30-8**, Glutaraldehyde **151-51-9**, Carbodiimide
512-69-6, **Raffinose 578-19-8**, Diaspirin
1892-57-5 53188-07-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(Hb-antioxidant conjugates)
RN 111-30-8 HCAPLUS
CN Pentanedial (9CI) (CA INDEX NAME)

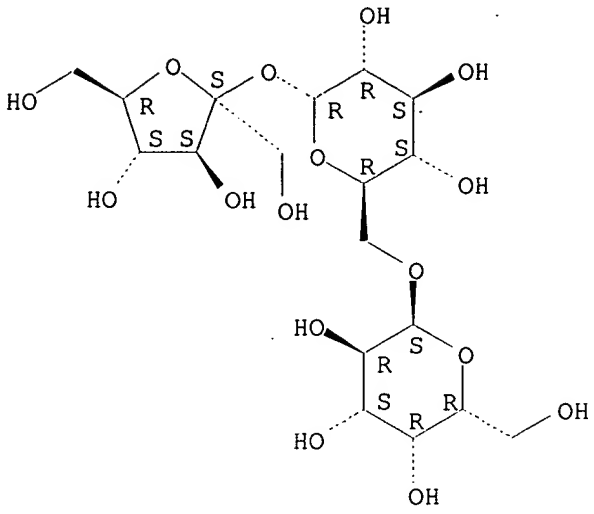
OHC—$(CH_2)_3$—CHO

RN 151-51-9 HCAPLUS
CN Methanediimine (9CI) (CA INDEX NAME)

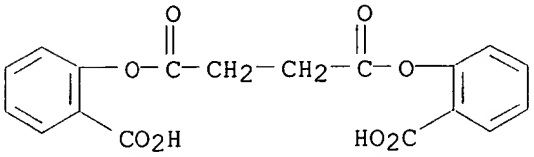
HN═C═NH

RN 512-69-6 HCAPLUS
CN .alpha.-D-Glucopyranoside, .beta.-D-fructofuranosyl O-.alpha.-D-galactopyranosyl-(1.fwdarw.6)- (9CI) (CA INDEX NAME)

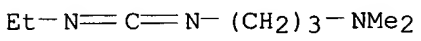
Absolute stereochemistry. Rotation (+).



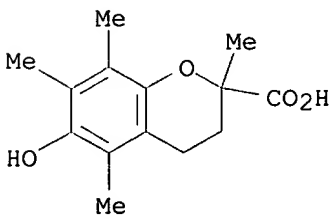
RN 578-19-8 HCAPLUS
CN Butanedioic acid, bis(2-carboxyphenyl) ester (9CI) (CA INDEX NAME)



RN 1892-57-5 HCAPLUS
CN 1,3-Propanediamine, N'-(ethylcarbonimidoyl)-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 53188-07-1 HCAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)



L109 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS
AN **1999:722875** HCAPLUS
DN **131:341966**
TI **Hemoglobin**-haptoglobin complexes for hepatic drug delivery
IN **Adamson, J. Gordon**; Wodzinska, Jolanta Maria; Moore, Marie

Sylvie Celine
PA **Hemosol Inc., Can.**
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-00
CC **63-5** (Pharmaceuticals)
Section cross-reference(s): 8, 9
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9956723	A2	19991111	WO 1999-CA396	19990430
	WO 9956723	A3	20000106		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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	AU 9936960	A1	19991123	AU 1999-36960	19990430
	EP 1075280	A2	20010214	EP 1999-919005	19990430
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	JP 2002513747	T2	20020514	JP 2000-546750	19990430
PRAI	CA 1998-2236344	A	19980430		
	WO 1999-CA396	W	19990430		

AB Construct-complexes of a **Hb**, a hepatocyte modifying substance bound to the **Hb**, and a haptoglobin bound to the **Hb**, are provided, for administration to mammalian patients. The construct-complex may be formed ex vivo , or a **Hb**-hepatocyte modifying substance combination may be administered to the patient so that haptoglobin in the mammalian body bonds thereto to form the construct-complex in vivo . Disorders of the liver may be diagnosed and treated using construct-complexes described herein.

ST liver delivery disease diagnosis **Hb** complex haptoglobin
IT Anti-inflammatory agents
Antimicrobial agents
Antioxidants
Antitumor agents
Antiviral agents
Blood plasma
Coupling agents
Cytoprotective agents
Fluorescent substances
Liver, disease
Parasiticides
Radioactive substances
(**Hb**-haptoglobin complexes for hepatic drug delivery)
IT Haptoglobin
Hemoglobins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(**Hb**-haptoglobin complexes for hepatic drug delivery)
IT Antitoxins
Enzymes, biological studies
Nucleic acids

Proteins, general, biological studies
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**Hb**-haptoglobin complexes for hepatic drug delivery)

IT Fibrosis
(agents affecting; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Diagnosis
(agents; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Haptoglobin
Hemoglobins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(complexes; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Liver
(drug delivery to; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Receptors
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(haptoglobin, metastatic cells bearing; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Drug delivery systems
(hepatic; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Liver
(hepatocyte, drug delivery to; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Cytoprotective agents
(hepatoprotectants; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab., agents affecting; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Antitumor agents
(metastasis; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT Crosslinking agents
(trifunctional; **Hb**-haptoglobin complexes for hepatic drug delivery)

IT 90-34-6, Primaquine 110-60-1, 1,4-Butanediamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**Hb**-haptoglobin complexes for hepatic drug delivery)

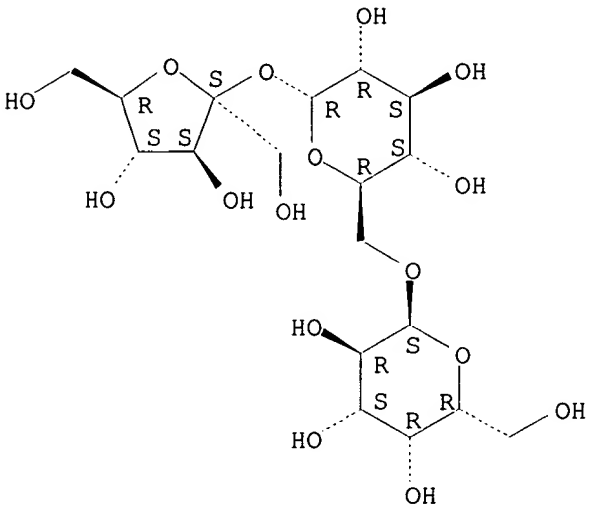
IT 249615-51-8DP, **conjugates**
RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**Hb**-haptoglobin complexes for hepatic drug delivery)

IT 107091-89-4, Thiazole orange
RL: PRP (Properties); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(**Hb**-haptoglobin complexes for hepatic drug delivery)

IT **512-69-6, Raffinose** 10121-91-2, Monodansyl cadaverine
20166-34-1, reactions 63368-54-7, 5-Iodoacetamido fluorescein
65989-10-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(**Hb**-haptoglobin complexes for hepatic drug delivery)

IT 25104-18-1, Poly-L-lysine 38000-06-5, Poly-L-lysine
RL: RCT (Reactant); RACT (Reactant or reagent)
(**conjugation** of; **Hb**-haptoglobin complexes for hepatic drug delivery)
IT 144181-06-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(crosslinking agent; **Hb**-haptoglobin complexes for hepatic drug delivery)
IT **512-69-6, Raffinose**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**Hb**-haptoglobin complexes for hepatic drug delivery)
RN 512-69-6 HCAPLUS
CN .alpha.-D-Glucopyranoside, .beta.-D-fructofuranosyl O-.alpha.-D-galactopyranosyl-(1.fwdarw.6)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L109 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2002 ACS
AN **1983:166880** HCAPLUS
DN **98:166880**
TI Oxygen carrier for blood substitutes
IN Iwashita, Yuji; Iwasaki, Keiji; Ajisaka, Katsumi
PA Ajinomoto Co., Inc., Japan
SO Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW
DT Patent
LA English
IC A61K037-14; C08G065-32
CC **63-3** (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 67029	A2	19821215	EP 1982-302826	19820602
	EP 67029	A3	19830803		
	EP 67029	B1	19860430		
	R: DE, FR, GB				
	JP 57206622	A2	19821218	JP 1981-89315	19810610
	JP 02006337	B4	19900208		
	US 4412989	A	19831101	US 1982-384606	19820603
PRAI	JP 1981-89315		19810610		

AB An O carrier is prepd. by introducing at least 1 CO2H group into a polyalkylene glycol or polyether and covalently bonding the polymer to an

NH2 group of a **Hb** or a **Hb** deriv. by amidation. Thus, monomethoxy polyethylene glycol succinate [79934-70-6] was stirred overnight at room temp. with N-hydroxysuccinimide in DMF in the presence of dicyclohexylcarbodiimide, the dicyclohexylurea ppt. was sepd. by filtration, and Et2O was added to the filtrate to obtain monomethoxy polyethylene glycol mono(succinimidyl succinate) [78274-32-5], which was filtered and added at 0.degree. to a pH 8.5 soln. of the pyridoxal 5-phosphate deriv. of **Hb**. The product was purified by ultrafiltration, and freeze-dried to give a modified **Hb** with a degree of substitution of 6.0 and a mol. wt. of 95,000. The half-lives of the **Hb**-polyether complexes in the circulatory system of rats were 4-7-fold those of **Hb**, and the complexes showed good ability to deliver O to the tissues.

ST **Hb** polyether complex oxygen carrier; blood substitute oxygen carrier

IT Polyethers
Polyoxyalkylenes
RL: PREP (Preparation)
(**Hb** complexes, prepn. of, as oxygen carriers for blood substitutes)

IT Blood substitutes and Plasma expanders
(**Hb**-polyether complexes as oxygen carriers in, prepn. of)

IT **Hemoglobins, carbonyl-**
RL: PREP (Preparation)
(pyridoxalated, reaction products with polyethers, prepn. of, as oxygen carriers for blood substitutes)

IT **Hemoglobins**
RL: PREP (Preparation)
(derivs., reaction products with polyethers, prepn. of, as oxygen carriers for blood substitutes)

IT 7782-44-7D, **Hb**-polyether complexes
RL: PROC (Process)
(dissocn. of, blood substitute in relation to)

IT **87-86-5**
RL: RCT (Reactant)
(esterification by, of polyethylene glycol adipate)

IT 37684-51-8
RL: RCT (Reactant)
(esterification of, by hydroxysuccinimide)

IT 39828-93-8
RL: RCT (Reactant)
(esterification of, by nitrophenol)

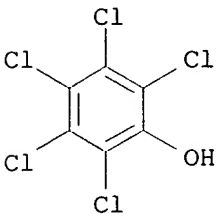
IT 79934-70-6
RL: RCT (Reactant)
(esterification of, with hydroxysuccinimide)

IT 68379-41-9
RL: RCT (Reactant)
(esterification of, with pentachlorophenol)

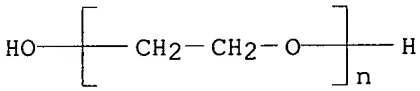
IT **25322-68-3**
RL: RCT (Reactant)
(esterification of, with succinic anhydride)

IT 54-47-7DP, **Hb** derivs., reaction products with polyethers
56-73-5DP, **Hb** derivs., reaction products with polyethers
1981-49-3DP, **Hb** derivs., reaction products with polyethers
40225-35-2DP, **Hb** derivs., reaction products with polyethers
42253-87-2DP, **Hb** derivs., reaction products with polyethers
78274-32-5DP, reaction products with **Hb** derivs. 85419-89-2DP, reaction products with carbonylHbs 85419-90-5DP, reaction products with **Hb** derivs. 85419-91-6DP, reaction products with **Hb** derivs. 85419-92-7DP, reaction products with **Hb** derivs. 85419-93-8DP, reaction products with carbonylHb derivs. 85419-94-9DP, reaction products with **Hb** derivs.
RL: PREP (Preparation)

(prepn. of, as oxygen carriers for blood substitutes)
IT 530-62-1
RL: RCT (Reactant)
(reaction of, with monomethoxy polyethylene glycol succinate)
IT 123-56-8
RL: RCT (Reactant)
(reaction of, with monomethoxypolyethylene glycol succinate)
IT **87-86-5**
RL: RCT (Reactant)
(esterification by, of polyethylene glycol adipate)
RN 87-86-5 HCAPLUS
CN Phenol, pentachloro- (8CI, 9CI) (CA INDEX NAME)



IT **25322-68-3**
RL: RCT (Reactant)
(esterification of, with succinic anhydride)
RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy- (9CI) (CA INDEX NAME)



=> fil reg
FILE 'REGISTRY' ENTERED AT 17:09:16 ON 28 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 26 AUG 2002 HIGHEST RN 444986-65-6
DICTIONARY FILE UPDATES: 26 AUG 2002 HIGHEST RN 444986-65-6

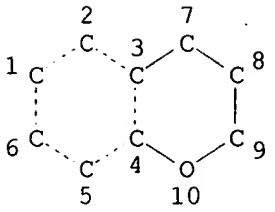
TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l39
L28 STR



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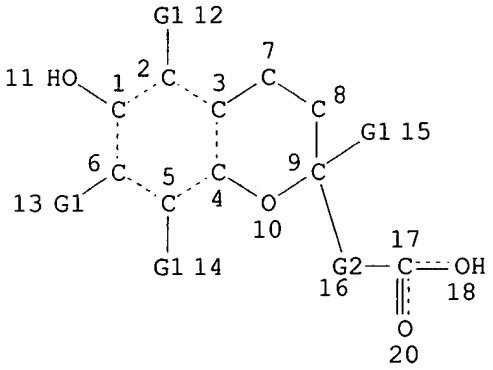
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
L30 34574 SEA FILE=REGISTRY SSS FUL L28
L32 STR



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REP G2=(0-1) AK
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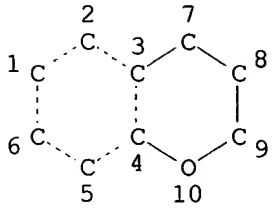
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 9
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L34 68 SEA FILE=REGISTRY SUB=L30 CSS FUL L32
L35 27 SEA FILE=REGISTRY ABB=ON PLU=ON C14H18O4 AND L34
L36 25 SEA FILE=REGISTRY ABB=ON PLU=ON L35 AND 2 5 7 8
L37 25 SEA FILE=REGISTRY ABB=ON PLU=ON L36 AND TETRAMETHYL
L38 12 SEA FILE=REGISTRY ABB=ON PLU=ON L37 NOT (MXS/CI OR COMPD)
L39 8 SEA FILE=REGISTRY ABB=ON PLU=ON L38 NOT (14C# OR 13C# OR ION)

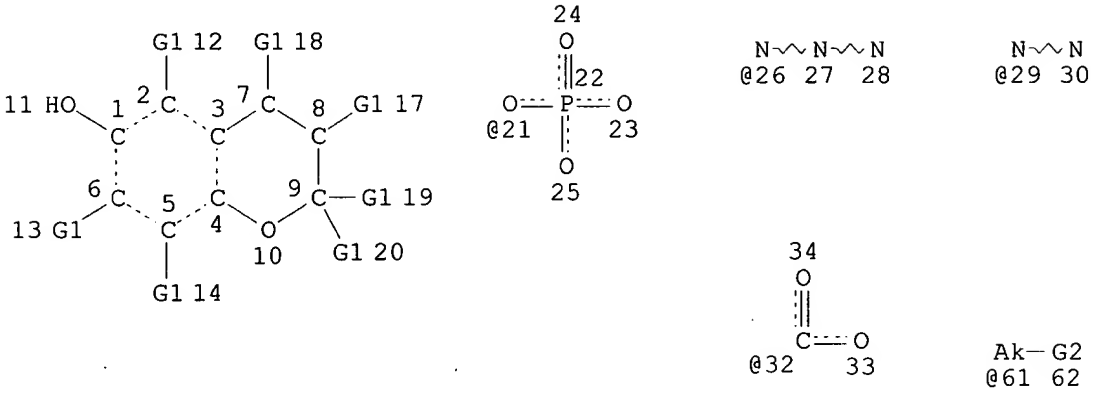
=> d sta que l43
L28 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
L30 34574 SEA FILE=REGISTRY SSS FUL L28
L40 STR



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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 9
NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE
L42 865 SEA FILE=REGISTRY SUB=L30 CSS FUL L40
L43 696 SEA FILE=REGISTRY ABB=ON PLU=ON L42 AND 1/NC

=> d his

(FILE 'HOME' ENTERED AT 15:37:39 ON 28 AUG 2002)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 15:37:49 ON 28 AUG 2002
E HEMOGLOBIN/CN
E HEMOGLOBIN
L1 2888 S E3,E6,E7

FILE 'HCAPLUS' ENTERED AT 15:38:37 ON 28 AUG 2002

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                E ADAMSON J/AU
L2           36 S E3,E6,E7
L3            2 S E17
                E MCINTOSH G/AU
L4           15 S E3
L5            1 S E24
                E MC INTOSH G/AU
L6           53 S L2-L5
L7        93373 S HEMOGLOBIN OR HEMOPROTEIN
L8            7 S L6 AND L7
                E HEMOSOL/PA,CS
L9           32 S E3-E14
L10          23 S L7 AND L9
                E HEMOGLOBIN/CT
                E E3+ALL
L11        2644 S E1
                E E2+ALL
L12       39033 S E4,E3+NT
                E HEMOGLOBIN/CW
L13       36770 S E3,E4
                E HEMOPROTEIN/CT
                E E4+ALL
L14        2460 S E2
                E HEMOPROTEIN/CW
L15        2460 S E4
L16          23 S L6,L9 AND L11-L15
L17          26 S L8,L10,L16
L18        8933 S L1
L19           4 S L6 AND L18
L20          26 S L17,L19
L21           2 S L20 AND ANTIOXID?
L22           2 S L21 AND CONJUGAT?
L23           1 S L22 NOT HAPTOGLOBIN
L24          25 S L20 NOT L23
                SEL RN L23

     FILE 'REGISTRY' ENTERED AT 15:58:00 ON 28 AUG 2002
L25          18 S E1-E18
L26             STR
L27          50 S L26
L28             STR L26
L29          50 S L28
L30       34574 S L28 FUL
L31           3 S L25 AND L30
L32             STR L26
L33           3 S L32 CSS SAM SUB=L30
L34          68 S L32 CSS FUL SUB=L30
                SAV TEMP L34 KWON926/A
L35          27 S C14H18O4 AND L34
L36          25 S L35 AND 2 5 7 8
L37          25 S L36 AND TETRAMETHYL
L38          12 S L37 NOT (MXS/CI OR COMPD)
L39           8 S L38 NOT (14C# OR 13C# OR ION)
L40             STR L32
L41          50 S L40 CSS SAM SUB=L30
L42         865 S L40 CSS FUL SUB=L30
                SAV TEMP L42 KWON926A/A
L43         696 S L42 AND 1/NC
L44          20 S L43 AND IDS/CI
L45          16 S L44 NOT N/ELS
L46          13 S L45 NOT OC4/ES
L47          11 S L46 NOT PROPANETRICARBOXYLIC
L48          10 S L47 NOT C29H50O4
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L49           5 S 36118-45-3 OR 120-72-9 OR 120-73-0 OR 50-81-7 OR 56631-56-2

     FILE 'HCAPLUS' ENTERED AT 16:33:37 ON 28 AUG 2002
L50         783 S L39
L51          11 S L47
L52       13756 S L43
L53       57334 S L49
L54        1207 S TROLOX
                E ANTIOXIDANT/CT
                E E11+ALL
L55       44113 S E5
                E PHENOL/CT
                E PHENOLIC/CT
                E PHENOLS/CT
                E E3+ALL
L56       39759 S E7
L57      495459 S E7+NT
                E PYRAZOLINE
L58        5176 S E3
                E CAROTENOID
L59       24640 S E3
                E CAROTENE/CT
                E E4+ALL
L60       27122 S E8,E9,E7+NT
                E E40+ALL
L61       30196 S E8+NT
                E RETINOID
L62       10616 S E3
                E QUINONE
L63       37568 S E3
L64       47410 S INDOLE
L65       35719 S PURINE
L66       90913 S ASCORBIC ACID OR VITAMIN(S)C
                E STEROID/CT
                E E70+ALL
L67       51921 S E2
                E ALKALOID/CT
                E E21+ALL
L68       33176 S E2
L69      121979 S E2+NT
L70      212261 S STEROID OR ALKALOID
L71        5491 S L50-L70 AND L7,L11-L15,L18
L72         191 S L71 AND ?CONJUGAT?
L73          15 S L72 AND 63/SC

     FILE 'REGISTRY' ENTERED AT 16:41:25 ON 28 AUG 2002
L74           6 S 111-30-8 OR 578-19-8 OR 512-69-6 OR 1892-57-5 OR 151-51-9 OR

     FILE 'HCAPLUS' ENTERED AT 16:44:18 ON 28 AUG 2002
L75          88 S L74 AND L71
L76          30 S L75 AND L72
L77           4 S L73 AND L76
                SEL DN AN 1 2
L78           2 S E1-E6
L79          37 S L73,L76 NOT L77
                SEL DN AN 6 12 28
L80           3 S L79 AND E7-E15
L81           3 S L6,L9 AND L50-L70
L82           2 S L81 NOT HIV
L83          24 S L75 AND 63/SC
L84          24 S L73,L83 NOT L79
L85          22 S L84 NOT L78,L80,L82
                SEL DN AN 4 22
```

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L86           2 S L85 AND E16-E21
L87           4 S L82,L86
L88        1066 S L50-L54 AND L71
L89          63 S L88 AND 63/SC
L90           3 S L89 AND ?CONJUGAT?
L91          60 S L89 NOT L90
                SEL DN AN 1
L92           1 S L91 AND E22-E24
L93           4 S L87,L92 AND L2-L24,L50-L73,L75-L92

     FILE 'REGISTRY' ENTERED AT 17:02:48 ON 28 AUG 2002
L94           1 S RAFFINOSE/CN

     FILE 'HCAPLUS' ENTERED AT 17:03:00 ON 28 AUG 2002
L95        7486 S L94 OR RAFFINOSE
L96          69 S L95 AND L7,L11-L15,L18
L97           6 S L96 AND L50-L70
L98           2 S L97 AND 63/SC
L99           4 S L93,L98
L100         11 S L96 AND ?CONJUGAT?
L101          9 S L100 NOT L99
L102          2 S L99 AND L100
L103          4 S L99,L102
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 17:06:38 ON 28 AUG 2002
L104         15 S E25-E39

     FILE 'HCAPLUS' ENTERED AT 17:07:00 ON 28 AUG 2002
L105          4 S L23,L103
L106          4 S L105 AND L2-L24,L50-L73,L75-L93,L95-L103

     FILE 'REGISTRY' ENTERED AT 17:08:05 ON 28 AUG 2002
L107          1 S 41903-66-6

     FILE 'HCAPLUS' ENTERED AT 17:08:11 ON 28 AUG 2002
L108          1 S L107 AND L7,L11-L15,L18
L109          4 S L106,L108

     FILE 'HCAPLUS' ENTERED AT 17:08:57 ON 28 AUG 2002

     FILE 'REGISTRY' ENTERED AT 17:09:16 ON 28 AUG 2002

=> fil wpix
FILE 'WPIX' ENTERED AT 17:17:48 ON 28 AUG 2002
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FILE LAST UPDATED: 23 AUG 2002              <20020823/UP>
MOST RECENT DERWENT UPDATE           200254   <200254/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> SLART (Simultaneous Left and Right Truncation) is now
    available in the /ABEX field. An additional search field
    /BIX is also provided which comprises both /BI and /ABEX <<<

>>> The BATCH option for structure searches has been
    enabled in WPINDEX/WPIDS and WPIX  <<<

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<
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http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d all abeq tech abex tot

L117 ANSWER 1 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 2002-362425 [39] WPIX
DNC C2002-102647
TI Oxygen carrying compound, useful as blood substitute, comprises low molecular weight hemoglobin conjugate covalently joined to polysaccharide.
DC A96 B04
IN TSAI, S; WONG, J T
PA (DEXT-N) DEXTRO SANG CORP; (TSAI-I) TSAI S P
CYC 97
PI WO 2002024751 A1 20020328 (200239)* EN 35p C07K014-805 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
CA 2319966 A1 20020319 (200239) EN A61K038-42 <--
AU 2001093554 A 20020402 (200252) C07K014-805 <--
ADT WO 2002024751 A1 WO 2001-CA1329 20010919; CA 2319966 A1 CA 2000-2319966 20000919; AU 2001093554 A AU 2001-93554 20010919
FDT AU 2001093554 A Based on WO 200224751
PRAI CA 2000-2319966 20000919
IC ICM **A61K038-42; C07K014-805**
ICS **A61K047-48**; C08B037-00
AB WO 200224751 A UPAB: 20020621
NOVELTY - An oxygen carrying compound comprises a conjugate of hemoglobin covalently joined to a polysaccharide. The conjugate has an average molecular weight of 50 - 500 (preferably 89 - 116) kD.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for preparation of oxygen carrying compound involving:
(1) reacting the polysaccharide with a bromine compound to provide activated polysaccharide;
(2) filtering the activated polysaccharide with a first filter;
(3) reacting the activated polysaccharide with hemoglobin to provide a coupled dextran-hemoglobin molecule; and
(4) filtering the dextran-hemoglobin molecule with a second filter.
USE - As a blood substitute or plasma expander in mammals.
ADVANTAGE - The compound has an erythrocyte sedimentation rate (ESR) of less than 20 (preferably 1) mm/hr, using Wintrobe's Method and a renal excretion rate (EXC) of less than 1 (preferably less than 0.2)%.
Dwg.0/5
FS CPI
FA AB; DCN
MC CPI: A03-A01; A10-E01; A12-V; A12-V0 ...14-F11
TECH UPTX: 20020621
TECHNOLOGY FOCUS - POLYMERS - Prefer... further involves filtering the dextran-hemog... ...hird filter. Preferred Components: The polysaccha... ...erage molecular weight of 20 kD. The first ... ...hat results in a retentate having a molecular wei... ...referably greater than 500) kD. The second filt... ...a pore size that results in a retentate having a molecular weight of greater than 500 kD. The third filter has a pore size that results in a retentate having a molecular

Brian - These patents are broader than those from CA - Hb conjugate + ...

weight of greater than 80 kD.

TECHNOLOGY FOCUS - BIOLOGY - The hemoglobin is stroma-free hemoglobin.

ABEX

EXAMPLE - DxBr (16.7 g) was dissolved in 1% stroma-free hemoglobin solution (5 l). Sodium bicarbonate buffer was added to a final concentration of 0.1 M and pH was adjusted to 9.5 with 1 M sodium hydroxide. The solution mixture was first sterilized, stirred and the coupling reaction was proceeded at 4 degrees C for 16 hours. beta-Mercaptoionic acid (16 mM) was added to react with any residual bromo groups and to stop the coupling reaction. The solution was dialyzed against 10mm phosphate buffered saline, pH 7.4, 60 minutes later to clear any residual reactants such as beta-Mercaptoionic acid, bromo groups. A dialysis bag was used, while a 10 kD filter cartridge was used for the diafiltration in pilot scale to give Dextran-Hemoglobin conjugate. Commercial guinea pigs were fasted and anesthetized by intraperitoneal injection. 70% MBO was bled through carotid artery during the first 10 minutes, during which time the blood pressure changed from 85 - 30 mmHg. Subsequently, 0.2 - 0.5 ml was bled occasionally for the following 80 minutes to keep the blood pressure at, 25 - 30 mmHg. At 90 minutes, hemoglobin (a) or fractionated conjugate (b) in kidney dialysis was infused over 60 minutes. Survival (%) for (a)/(b) was as 100/50.

L117 ANSWER 2 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 2001-517046 [57] WPIX
DNC C2001-154657
TI A porphyrin metal complex-albumin polymer inclusion compound useful for oxygen fluid therapy.
DC B04
PA (TSUC-I) TSUCHIDA H
CYC 1
PI JP 2001131200 A 20010515 (200157)* 9p C07K014-805 <--
ADT JP 2001131200 A JP 1999-318702 19991109
PRAI JP 1999-318702 19991109
IC ICM **C07K014-805**
ICS A61K038-00; **A61K047-48**; A61P007-00
ICA A61K031-407; C07D487-22
AB JP2001131200 A UPAB: 20011005
NOVELTY - A porphyrin metal complex-albumin polymer inclusion compound (I) in which a substituted porphyrin metal complex having a transition metal of the 4th and the 5th period in periodic table as the central coordinated metal is included in an albumin polymer where at least two albimun molecules are intermolecularly crosslinked by a crosslinker through the cysteine residue of albumin.

DETAILED DESCRIPTION - AN INDEPENDENT CLAIM is also included for an oxygen fluid therapy comprising (I).

ACTIVITY - None given.

MECHANISM OF ACTION - None given.

USE - The complex is used in the oxygen liquid therapy.

Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-B04D; B04-N02; B05-A03; B06-D18; B14-F03; B14-F11; B14-K01
ABEX

EXAMPLE - Human serum albumin (8.8 ml) and bismaleimidohexane (9.1 mg) were dissolved in phosphate-buffered physiological saline water (18.8 ml and 3 ml respectively). The bismaleimidohexane solution was irradiated by ultrasonic wave for several seconds. Each solution were replaced by nitrogen and mixed together slowly and the mixture was stirred at 4degreesC for 12 hours. It was purified by a gel filtration. The resultant albumin dimer had a molecular weight of about 130 kDa. Aqueous ascorbic acid solution was added to ethanol solution (12 ml) of 2-(8-(2-methyl-1-imidazolyl))octanoyloxymethyl)-5,10,15,20-

tetrakis(alpha,alpha,alpha,alpha,-O-pivalamidophenylporphinato iron (III) complex (16 microM) under carbon monoxide atmosphere to reduce the central iron of porphyrin to +2 valent and to give a carbon monoxide complex. The ethanol solution was mixed with 1/30 mM phosphate buffer (36 ml) of 1 microM human serum albumin dimer and the mixture was dialyzed against physiological saline water to give a dispersion of 2-(8'-(2-methyl-1-imidazolyl))octanoyloxymethyl)-5,10,15,20-tetrakis(alpha,alpha,alpha,alpha ,-O-pivalamidophenyl)porphinato iron (II) carbon monoxide complex-albimun dimer inclusion compound.

L117 ANSWER 3 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 2001-255481 [26] WPIX
DNC C2001-076820
TI Blood substitute as óxygen transporter, composition for its preparation and method of polymeric modified hemoglobin preparation.
DC B04
IN BELOV, E V; BYSTROVA, I M; GERBUT, K A; GONCHAROV, A V; GUDKIN, L R; KHANEVICH, M D; KOCHETYGOV, N I; KUZNETSOVA, N P; MISHAEVA, R N; MOLOKOVSKAYA, I E; PANARIN, E F; SELIVANOV, E A
PA (ASHI-R) AS RUSSIA HIGH MOL WT CPDS INST; (HAEM-R) HAEMATOLOGY TRANSFUSION RES INST
CYC 1
PI RU 2162707 C2 20010210 (200126)* A61K038-42 <--
ADT RU 2162707 C2 RU 1999-106110 19990324
PRAI RU 1999-106110 19990324
IC ICM A61K038-42
ICS A61K009-08; A61K009-19
AB RU 2162707 C UPAB: 20010515
NOVELTY - A blood substitute as an oxygen transporter that is an aqueous solution containing the following components, (weight%): polymeric modified hemoglobin, 0.9-1.1; sodium chloride, 1.0-1.2; glucose, 0.68-0.83; ascorbic acid, 0.023-0.027; and water up to 100. The invention relates also to the composition for preparing a blood substitute as oxygen transporter containing grams per single therapeutic dose (400 ml of solution): polymeric modified hemoglobin, 3.6-4.4; sodium chloride, 0.7-0.9; glucose, 2.7-3.3; ascorbic acid, 6 deg. C-0.11. Polymeric modified hemoglobin is prepared by interaction of deoxyhemoglobin with glutaric aldehyde modified at pH 6.4-6.6 and 4-6 deg. C with substance of an order including dicarboxylic amino acid and sodium bisulfite.
USE - Medicine, hematology.
ADVANTAGE - Efficiency of proposed blood substitute is comparable with that of gaseous transport with human blood. 4 cl, 3 tbl, 2 ex Dwg.0/0
FS CPI
FA AB
MC CPI: B04-B04D; B12-M05

L117 ANSWER 4 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 2001-135308 [14] WPIX
DNC C2001-057629
TI New conjugate having modified erythropoietin glycoprotein useful for stimulating red blood cell production and for treating diseases correlated with anemia in chronic renal failure, AIDS or cancer patients.
DC A96 B04
IN BAILON, P S; SEBASTIAN BAILON, P
PA (HOFF) HOFFMANN LA ROCHE & CO AG F
CYC 37
PI NO 2000003372 A 20010103 (200114)* C07K017-10
CA 2310536 A1 20010102 (200114) EN C07K014-505
DE 10031839 A1 20010201 (200114) C07K014-505
GB 2353281 A 20010221 (200115) C07K017-08
JP 2001064300 A 20010313 (200118) 16p C07K014-505
EP 1064951 A2 20010103 (200120)B EN 16p A61K047-48 <--

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

ZA	2000003282	A	20010328 (200121)	31p	A61K000-00	
FR	2795734	A1	20010105 (200124)		C07K014-505	
HU	2000002553	A2	20010328 (200124)		C12P021-02	
AU	2000042744	A	20010104 (200128)		C07K014-575	
CN	1280137	A	20010117 (200128)		C07K014-505	
AU	736067	B	20010726 (200149)		C07K014-575	
KR	2001049676	A	20010615 (200171)		C07K014-505	
BR	2000002276	A	20011211 (200203)		A61K038-42	<--
NZ	505454	A	20011221 (200210)		C07K017-08	
CZ	2000002386	A3	20020417 (200231)		A61K047-48	<--
SK	2000000987	A3	20020604 (200247)		A61K047-48	<--

ADT NO 2000003372 A NO 2000-3372 20000628; CA 2310536 A1 CA 2000-2310536 20000628; DE 10031839 A1 DE 2000-10031839 20000630; GB 2353281 A GB 2000-16205 20000630; JP 2001064300 A JP 2000-201525 20000703; EP 1064951 A2 EP 2000-113115 20000628; ZA 2000003282 A ZA 2000-3282 20000629; FR 2795734 A1 FR 2000-8609 20000703; HU 2000002553 A2 HU 2000-2553 20000630; AU 2000042744 A AU 2000-42744 20000628; CN 1280137 A CN 2000-107889 20000629; AU 736067 B AU 2000-42744 20000628; KR 2001049676 A KR 2000-36976 20000630; BR 2000002276 A BR 2000-2276 20000703; NZ 505454 A NZ 2000-505454 20000628; CZ 2000002386 A3 CZ 2000-2386 20000623; SK 2000000987 A3 SK 2000-987 20000627

FDT AU 736067 B Previous Publ. AU 200042744

PRAI US 1999-166151P 19991117; US 1999-142254P 19990702; US 1999-150225P 19990823; US 1999-151548P 19990831

IC ICM A61K000-00; **A61K038-42**; **A61K047-48**; C07K014-505; C07K014-575; C07K017-08; C07K017-10; C12P021-02

ICS A61K038-17; A61K038-18; A61K038-22; A61P007-00; A61P007-06; A61P013-12; A61P031-00; A61P035-00; C07H000-00; C07K001-107; C07K014-59; C07K019-00; C12N015-12

AB EP 1064951 A UPAB: 20010410 ABEQ treated as Basic

NOVELTY - A conjugate comprising an erythropoietin (EPO) glycoprotein is new. The EPO has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

DETAILED DESCRIPTION - A conjugate comprising an erythropoietin (EPO) glycoprotein is new. The EPO has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

The EPO comprises human EPO (hEPO) or its analogs, which has the sequence of hEPO modified by the addition of 1-6 glycosylation sites or a rearrangement of at least one glycosylation site.

The glycoprotein is covalently linked to n polyethylene glycol groups of formula CO-(CH2)x-(OCH2CH2)m-OR (I).

R = lower alkyl;

x = 2 or 3;

m = 450-900 and

n = 1-3.

n And m are chosen so that the molecular weight of the conjugate minus the erythropoietin glycoprotein is 20-100 kilodaltons. The CO of each polyethylene glycol group forms an amide bond with one of the amino groups.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising conjugates, each of the conjugates comprising the erythropoietin glycoprotein described above, the percentage of conjugates (where n =1) is at least 90% and

(2) preparation of (I).

ACTIVITY - Antianemic; immunostimulant; cytostatic; nephrotropic.

MECHANISM OF ACTION - Bone marrow cell stimulator; erythroid progenitor stimulator.

In separate experiments, a single dose of unmodified EPO (25 ng of EPO), PEG(SBA)-EPO mixture (10 ng of conjugate), mono- and di-pegylated EPOs (10 ng conjugate), PEG(SPA)-EPO (10 ng of conjugate) and buffer solution were administered to mice. The results showed the superior activity and the prolonged half life of the pegylated EPO species indicated by the increased amounts of reticulocytes and the shift of the reticulocytes count maximum using the same dose per mouse (10 ng), compared to a dose of 25 ng for unmodified EPO. At 96 h, the amount of reticulocytes for unmodified EPO, 30 kDa PEG(SPA)-EPO, mono-SBA-EPO, di-SBA-EPO, PEG-EPO conjugate mixture and the control buffer were 500, 1406, 1501, 926, 1338 and 697, respectively. At 144 hours, the number of reticulocytes were approx. 0, 535, 607, 665, 660 and 708, respectively.

USE - Useful for the treating or preventing diseases correlated with anemia in chronic renal failure, AIDS or cancer patients undergoing chemotherapy. The conjugate or composition is also useful for preparing medicaments for the treatment or prophylaxis of these diseases (all claimed).

ADVANTAGE - Compared to unmodified EPO and conventional PEG-EPO conjugates, the conjugates have an increased circulating half-life and plasma residence time, decreased clearance, and increased clinical activity in vivo.

Dwg.0/0

AB NO 200003372 A UPAB: 20010418

NOVELTY - A conjugate comprising an erythropoietin (EPO) glycoprotein is new. The EPO has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

DETAILED DESCRIPTION - A conjugate comprising an erythropoietin (EPO) glycoprotein is new. The EPO has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

The EPO comprises human EPO (hEPO) or its analogs, which has the sequence of hEPO modified by the addition of 1-6 glycosylation sites or a rearrangement of at least one glycosylation site.

The glycoprotein is covalently linked to n polyethylene glycol groups of formula CO-(CH2)x-(OCH2CH2)m-OR (I).

R = lower alkyl;

x = 2 or 3;

m = 450-900 and

n = 1-3.

n And m are chosen so that the molecular weight of the conjugate minus the erythropoietin glycoprotein is 20-100 kilodaltons. The CO of each polyethylene glycol group forms an amide bond with one of the amino groups.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising conjugates, each of the conjugates comprising the erythropoietin glycoprotein described above, the percentage of conjugates (where n =1) is at least 90% and

(2) preparation of (I).

ACTIVITY - Antianemic; immunostimulant; cytostatic; nephrotropic.

MECHANISM OF ACTION - Bone marrow cell stimulator; erythroid progenitor stimulator.

In separate experiments, a single dose of unmodified EPO (25 ng of EPO), PEG(SBA)-EPO mixture (10 ng of conjugate), mono- and di-pegylated EPOs (10 ng conjugate), PEG(SPA)-EPO (10 ng of conjugate) and buffer solution were administered to mice. The results showed the superior activity and the prolonged half life of the pegylated EPO species indicated by the increased amounts of reticulocytes and the shift of the reticulocytes count maximum using the same dose per mouse (10 ng), compared to a dose of 25 ng for unmodified EPO. At 96 h, the amount of reticulocytes for unmodified EPO, 30 kDa PEG(SPA)-EPO, mono-SBA-EPO,

di-SBA-EPO, PEG-EPO conjugate mixture and the control buffer were 500, 1406, 1501, 926, 1338 and 697, respectively. At 144 hours, the number of reticulocytes were approx. 0, 535, 607, 665, 660 and 708, respectively.

USE - Useful for the treating or preventing diseases correlated with anemia in chronic renal failure, AIDS or cancer patients undergoing chemotherapy. The conjugate or composition is also useful for preparing medicaments for the treatment or prophylaxis of these diseases (all claimed).

ADVANTAGE - Compared to unmodified EPO and conventional PEG-EPO conjugates, the conjugates have an increased circulating half-life and plasma residence time, decreased clearance, and increased clinical activity in vivo.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: A10-E08B; A12-V01; B04-C03C; B04-H07; B14-F04; B14-G01B

ABEQ EP 1064951 A UPAB: 20010410

NOVELTY - A conjugate comprising an erythropoietin (EPO) glycoprotein is new. The EPO has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

DETAILED DESCRIPTION - A conjugate comprising an erythropoietin (EPO) glycoprotein is new. The EPO has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

The EPO comprises human EPO (hEPO) or its analogs, which has the sequence of hEPO modified by the addition of 1-6 glycosylation sites or a rearrangement of at least one glycosylation site.

The glycoprotein is covalently linked to n polyethylene glycol groups of formula CO-(CH2)x-(OCH2CH2)m-OR (I).

R = lower alkyl;

x = 2 or 3;

m = 450-900 and

n = 1-3.

n And m are chosen so that the molecular weight of the conjugate minus the erythropoietin glycoprotein is 20-100 kilodaltons. The CO of each polyethylene glycol group forms an amide bond with one of the amino groups.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising conjugates, each of the conjugates comprising the erythropoietin glycoprotein described above, the percentage of conjugates (where n =1) is at least 90% and

(2) preparation of (I).

ACTIVITY - Antianemic; immunostimulant; cytostatic; nephrotropic.

MECHANISM OF ACTION - Bone marrow cell stimulator; erythroid progenitor stimulator.

In separate experiments, a single dose of unmodified EPO (25 ng of EPO), PEG(SBA)-EPO mixture (10 ng of conjugate), mono- and di-pegylated EPOs (10 ng conjugate), PEG(SPA)-EPO (10 ng of conjugate) and buffer solution were administered to mice. The results showed the superior activity and the prolonged half life of the pegylated EPO species indicated by the increased amounts of reticulocytes and the shift of the reticulocytes count maximum using the same dose per mouse (10 ng), compared to a dose of 25 ng for unmodified EPO. At 96 h, the amount of reticulocytes for unmodified EPO, 30 kDa PEG(SPA)-EPO, mono-SBA-EPO, di-SBA-EPO, PEG-EPO conjugate mixture and the control buffer were 500, 1406, 1501, 926, 1338 and 697, respectively. At 144 hours, the number of reticulocytes were approx. 0, 535, 607, 665, 660 and 708, respectively.

USE - Useful for the treating or preventing diseases correlated with anemia in chronic renal failure, AIDS or cancer patients undergoing chemotherapy. The conjugate or composition is also useful for preparing

medicaments for the treatment or prophylaxis of these diseases (all claimed).

ADVANTAGE - Compared to unmodified EPO and conventional PEG-EPO conjugates, the conjugates have an increased circulating half-life and plasma residence time, decreased clearance, and increased clinical activity in vivo.

Dwg.0/0

TECH UPTX: 20010410

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises condensing a polymeric compound of formula (II) with a EPO glycoprotein.

Preferred compounds: The conjugate is of formula (IA) or (IB).

P = the residue of the glycoprotein without the n amino group(s), which form amide linkage(s) with the polyethylene glycol group(s);

R = methyl;

m = 650-750 and

n = 1.

The glycoprotein is preferably hEPO, where the hEPO glycoprotein is expressed by endogenous gene activation. The glycoprotein has a sequence comprising 165 amino acids defined in the specification. The glycoprotein has the hEPO sequence, which has a modification selected from the following: Asn30Thr32; Asn51Thr53; Asn57Thr59; Asn69; Asn69Thr71; Ser68Asn69Thr71; Val87Asn88Thr90; Ser87Asn88Thr90; Ser87Asn88Gly89Thr90; Ser87Asn88Thr90Thr92; Ser87Asn88Thr90Ala162; Asn69Thr71Ser87Asn88Thr90; Asn30Thr32Val87Asn88Thr90; Asn89Ile90Thr91; Ser87Asn89Ile90Thr91; Asn136Thr138; Asn138Thr140; Thr125 or Pro124Thr125.

The glycoprotein also has a sequence comprising the hEPO sequence and a second sequence at the carboxy terminus of the human erythropoietin sequence, where the second sequence contains at least one glycosylation site. The second sequence comprises a sequences derived from the carboxy terminal sequence of the human chorionic gonadotropin. The glycoprotein has a sequence selected from:

(a) the sequence hEPO and the defined 28-amino acid sequence at the carboxy terminus of the hEPO sequence;

(b) the sequence in (a) modified by Ser87Asn88Thr90; or

(c) the sequence in (a) modified by Asn30Thr32Val87Asn88Thr90.

The glycoprotein also has the hEPO sequence modified by a rearrangement of at least one glycosylation site, where the rearrangement comprises deletion of any of the N-linked glycosylation sites in human erythropoietin and addition of an N-linked glycosylation site at position 88 of the hEPO sequence. In particular, the hEPO has a modification selected from: Gln24Ser87Asn88Thr90; Gln38Ser87Asn88Thr90; or Gln83Ser87Asn88Thr90.

Preferred composition: The percentage of conjugates in the composition, where n = 1, is at least 92%, preferably 96%.

ABEX

ADMINISTRATION - The dosage is 0.01-10 (preferably 0.1-1) mug/kg administered once weekly.

EXAMPLE - Erythropoietin (EPO)-producing CHO cell line (ATCC CRL8695) was prepared. A batch re-feed process was used, i.e. when the desired cell density was reached, 80% of the culture was harvested. The remaining culture was replenished with fresh culture medium and cultivated until the next harvest. The cells were removed by centrifugation or filtration and discarded. The EPO containing supernatant was in-line filtered, collected and purified. The purification of EPO-protein was disclosed in WO96/35718. The purified EPO was subjected to pegylation with mPEG-SBA (II: R = Me; x = 0-3 and m = 650-750)

To 100 mg of EPOsf (9.71 ml of a 10.3 mg/ml EPOsf stock, 5.48 micro-mol), 10 ml of 0.1 M potassium phosphate buffer (pH 7.5) containing 506 mg of 30 kDa methoxy-PEG-SBA (16.5 micro-mol) was added and mixed for 2 hours at room temperature (20-23degreesC). The final protein concentration was 5 mg/ml and the protein:PEG reagent ratio was 1:3. After 2 hours, the

reaction was stopped by adjusting the pH to 4.5 with glacial acetic acid and stored at -20degreesC, until ready for purification. The conjugate mixture was purified, then analyzed by SDS-PAGE, and the degree of pegylation determined. The purified conjugate mixture comprised of mono- and di-PEG-EPOsf and was free of unmodified EPOsf as determined by SDS-PAGE analysis. Conjugate mixture comprised 23.4 mg or 78% of the starting material.

L117 ANSWER 5 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 2000-611596 [58] WPIX
DNC C2000-183037
TI Composition with oxygen transporting capability comprises oxygen transporting molecules bonded to antioxidants, specifically hemoglobin-antioxidant composition useful e.g. in ischemic tissue reperfusion.
DC A96 B05
IN ADAMSON, G W; MCINTOSH, G A; ADAMSON, J G
PA (HEMO-N) HEMOSOL INC
CYC 93
PI WO 2000056367 A1 20000928 (200058)* EN 40p A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
CA 2266174 A1 20000918 (200062) EN C07K014-805 <--
AU 2000032690 A 20001009 (200103) A61K047-48 <--
EP 1163010 A1 20011219 (200206) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
KR 2001111571 A 20011219 (200238) A61K047-48 <--
ADT WO 2000056367 A1 WO 2000-CA299 20000320; CA 2266174 A1 CA 1999-2266174 19990318; AU 2000032690 A AU 2000-32690 20000320; EP 1163010 A1 EP 2000-910473 20000320, WO 2000-CA299 20000320; KR 2001111571 A KR 2001-711246 20010904
FDT AU 2000032690 A Based on WO 200056367; EP 1163010 A1 Based on WO 200056367
PRAI CA 1999-2266174 19990318
IC ICM **A61K047-48; C07K014-805**
ICS **A61K038-42**
AB WO 200056367 A UPAB: 20001114
NOVELTY - NOVELTY

A chemical composition has oxygen transporting capability and comprises biocompatible oxygen transporting molecules chemically bonded to one or more biocompatible antioxidants selected from e.g. non-enzymatic phenolic compounds, pyrazolines, carotenoid and retinoid compounds.

DETAILED DESCRIPTION - A chemical composition has oxygen transporting capability and comprises biocompatible oxygen transporting molecules chemically bonded to one or more biocompatible antioxidants selected from non-enzymatic phenolic compounds, pyrazolines, carotenoid and retinoid compounds, quinones, tetrapyrroles, indoles and aminoindoles, purine analogs, ascorbic acid, and steroid and alkaloid antioxidants.

INDEPENDENT CLAIMS are also included for the following:

(1) a process for preparing a hemoglobin composition having antioxidant properties;

(2) use of a chemical composition as above in the preparation or production of a biocompatible oxygen transporting liquid composition for administration to mammalian patients.

ACTIVITY - Antioxidant.

The degree of antioxidant protection by Hb-Trolox conjugates was compared to controls. Red blood cell lysis in the presence of free Trolox, free (control) hemoglobin, a mixture of free Trolox and hemoglobin, or hemoglobin Trolox conjugate was measured. Results showed that both the

Trolox and hemoglobin, alone, exhibited less protection than the corresponding hemoglobin-Trolox conjugates. The mixture of free Trolox and hemoglobin showed greater protection than an equal concentration of either compound alone, but still less protection than the corresponding hemoglobin-Trolox conjugates. Since the conjugate and the mixture had the same hemoglobin content, and the conjugate contained the same or less Trolox than the mixture, the greater activity of the conjugate suggested a synergistic effect, indicated by an increase in overall antioxidant activity due to conjugation.

USE - As hemoglobin-antioxidant compositions for administration to living beings for oxygen-transport purposes and antioxidant therapeutic purposes. The compositions may be used during temporary interruption of blood flow to tissue in surgical procedures e.g. cardiac surgery and organ preservation or transplantation. For reperfusion of ischemic tissue in blocked blood vessels in disease events such as myocardial infarction, thrombotic stroke, embolic vascular occlusions, angina pectoris and peripheral vascular insufficiency.

ADVANTAGE - The conjugation of extracellular hemoglobin to the antioxidant prevents oxygen-hemoglobin reactions that generate Met-hemoglobin and the oxygen free radical, superoxide (.O2-) which causes tissue damage, e.g. reperfusion injury. (This does not occur inside the red blood cell due to the presence of enzymes such as superoxide dismutase and catalase which convert superoxide to harmless by-products, water and oxygen). The oxidized antioxidant moiety conjugated to the hemoglobin may be reduced in vivo to a chemical state in which it is capable of further antioxidant activity and the conjugate recycled in the body for further action.

Dwg.0/4

FS CPI

FA AB; DCN

MC CPI: A12-V01; B03-A; B03-F; B04-A07A; B04-B04D2; B06-D01; B06-D09; B06-D18; B07-D08; B10-A06; B10-E02; B10-H01; B14-F05; B14-F11; B14-S08

TECH UPTX: 20001114

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Oxygen-transporting Substance: The oxygen transporting substance is a heme-protein macromolecule, especially a hemoglobin species. The hemoglobin of the conjugate is modified by a cross-linking agent. The hemoglobin is at least partially stabilized by the cross-linking agent to form stabilized tetrameric units. The hemoglobin of the conjugate is at least partially oligomerized into oligomers of up to 12 stabilized tetrameric units. Preferred Antioxidant: The antioxidant is a phenolic compound containing one or more groups of formula (I) and is especially (i) a polyphenolic, a substituted phenolic or a phenolic ether; (ii) a di-t-butylhydroxyphenylthio-substituted hydroxamic acid; (iii) a chroman-based compound such as a chromanol or a dihydrobenzofuranol; (iv) a flavanoid or isoflavanoid such as flavonone and dihydroflavanol; (v) a gallate; (vi) a catechol or catechol derivative; or (vii) a phenolic acid. The phenolic antioxidant is preferably a chromanol. The composition comprises the reaction product of an oxygen transporting compound and a 6-hydroxy chroman compound having antioxidant properties of formula (II), especially of formula (II').

n = 1-3.

In (I), the aromatic ring is optionally further substituted and optionally fused or linked to another carbocyclic or heterocyclic ring system.

R1-R3 = H, 1-8C alkyl or (CH2)n'X;

n' = 0-20;

R, R4-R6 = H, 1-20C alkyl, X or (CH2)mX;

X = a substituent containing a reactive functional group selected in conjunction with the chosen oxygen transporting compound so as to be capable of reacting with it to effect a chemical linkage of the oxygen transporting compound to the chroman compound;

provided that the chroman compound includes at least one functional group

X;
R' = H or 1-20C alkyl;
R1'-R3'= H or 1-4C alkyl;
R4' = a bond or 1-8C alkyl.
Preferably, X contains a functional group capable of reacting with amino acid residues of the protein chains of the heme protein macromolecule. Especially X = halo, carboxyl, amino, hydroxyl, thiol, azide, azo, aldehyde or phosphate.
Preferably at least on of R1-R3 is methyl and R4 = a bond.
Preferred Composition: The composition is a covalently linked conjugate of the chroman compound and human hemoglobin. The composition comprises a mixture of tetrameric stabilized hemoglobin units conjugated to the chroman carboxylic acid antioxidant and oligomers of 2-8 such stabilized hemoglobin units conjugated to the chroman carboxylic acid antioxidant.
Preparation: In (1), the method comprises chemically reacting hemoglobin and a hydroxy chroman compound as above (i.e.(II)) to form its covalently linked chemical conjugate. Preferably, prior to conjugation to the chroman carboxylic acid, the hemoglobin is reacted with a cross-linking reagent. The hemoglobin-chroman carboxylic acid conjugate is subsequently reacted with a hemoglobin cross-linking reagent, especially a polyaldehyde, particularly oxidatively ring opened-raffinose (o-raffinose). The hemoglobin is at least partially oligomerized by further reaction with o-raffinose. The reaction between hemoglobin and the hydroxy chroman compound is conducted in the presence of an activating compound. The activating compound is a carbodiimide, particularly 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC) and the chroman carboxylic acid antioxidant is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol (Trolox) (Ia).

TECHNOLOGY FOCUS - POLYMERS - The hemoglobin is modified or cross-linked with a polyaldehyde, glutaraldehyde, a diaspirin compound, a pyridoxyl compound or a trimesoyl compound. Preferably the hemoglobin is crosslinked with a polyaldehyde derived from oxidative ring-opening of a polysaccharide. The polysaccharide is especially raffinose. The hemoglobin-antioxidant conjugate is bonded to a biocompatible polymer. The biocompatible polymer is polyethylene glycol, a polysaccharide, a polyamino acid, or an insoluble support.

ABEX

SPECIFIC COMPOUNDS - The chroman carboxylic acid antioxidant is 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol. (Ia)

EXAMPLE - A series of experiments was conducted in which Trolox (TX) was conjugated to carbonmonoxyhemoglobin (COHb) using EDC as a coupling agent under conditions set out in a table. In each case, EDC, EDC and Trolox (TX) were combined in equimolar concentration in acetonitrile for 10 minutes at room temperature to give a stock TX-EDC solution (1.55 M). The TX-EDC solution was diluted with acetonitrile, when necessary, just prior to addition to Hb so that the final acetonitrile and TX-EDC content of the conjugation reaction was as indicated in the table (10 volume% in 8 cases and 1 volume % in 1 case). All conjugations were done in 40-50 mM MES buffer at pH 7 in 8 cases and pH 4 in one case. Reaction mixtures were held at 22 degreesC for up to 24 hours under CO gas. Samples were filtered and dialyzed against phosphate-buffered saline (PBS), pH 7.4. Hemoglobin-TX conjugates prepared as above were dialyzed against 50 mM Bis-Tris buffer, pH 6.8. 3 Equivalents o-raffinose dissolved in water were added to solutions of hemoglobin-Trolox to give a final hemoglobin concentration of 42 mg/ml. The mixtures were held under CO gas at 22 degreesC for 24 hours. The solutions were made 30 mM in sodium acetate, and 20 equivalents of aqueous dimethylamine borane relative to o-raffinose content were added. After 24 hours, the solutions were dialyzed against water, then PBS pH 7.4. Size exclusion chromatography indicated formation of intra- and intermolecularly cross-linked hemoglobin-TX species. If necessary, non-crosslinked hemoglobin species were removed by conventional

means, e.g. ultrafiltration.

L117 ANSWER 6 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 2000-526143 [48] WPIX
DNC C2000-156432
TI New nitric monoxide metabolite-polyoxyalkylene-hemoglobin complex useful as oxygen carrier in blood substitutes and organ perfusion solutions.
DC A25 A96 B04
IN KITABATAKE, A; NAKAI, K; SAKUMA, I; YASUKOHCHI, T
PA (NIOF) NOF CORP; (UYHO-N) UNIV HOKKAIDO; (NIOF) NIPPON OILS & FATS CO LTD
CYC 26
PI EP 1029551 A2 20000823 (200048)* EN 16p A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2000230000 A 20000822 (200055) 12p C07K014-805 <--
ADT EP 1029551 A2 EP 2000-102156 20000208; JP 2000230000 A JP 1999-67239 19990208
PRAI JP 1999-67239 19990208
IC ICM **A61K047-48; C07K014-805**
ICS A61K038-16; A61P007-00; A61P007-06
AB EP 1029551 A UPAB: 20001001
NOVELTY - New nitric monoxide metabolite-polyoxyalkylene-haemoglobin complex has a molecular weight of 100000-2000000 Da. The polyoxyalkylene derivative is bound to 10-30% of the bindable amino groups in the haemoglobin and the nitric monoxide metabolite is bound to 10-100% of the thiol groups of cysteine residues.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) an oxygen carrier solution comprising 10 to 200g/l of the novel complex and
(2) production of the complex.
USE - The complex is useful as an oxygen carrier in blood substitutes and organ perfusion solutions. The complex may be stored for a long period.
ADVANTAGE - The oxygen carrier solutions using the complex are cell-free, have good safety and do not cause hypertension on injection.
Dwg.0/4
FS CPI
FA AB; GI; DCN
MC CPI: A05-H01A; A10-E01; A12-V; A12-V02; B04-B04D2; B04-C03C; B10-A03; B14-F11
TECH UPTX: 20001001
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preparation: Production of the complex comprises e.g. reacting a polyoxyalkylene-hemaglobin complex with a nitric monoxide metabolite.
Preferred composition: The polyoxyalkylene derivative is of formula (1).
B = residue of a compound having 2-6 hydroxyl groups;
AO = 3-4C oxyalkylene;
R = 1-30C hydrocarbon or OH;
k, m = 0-500 and
k + m = 20-1000;
l, n = 0-10 and
l + n = 0-10;
a = 0-6;
b = 1-6 and
a + b = 2-6;
X = (CH2)c-COOY, OC-(CH2)d-COOY', (CH2)e-CHO or COZ;
c = 0-2;
Y = H, 4-nitrophenyl or N-hydroxysuccinimide;
d = 2-6;
Y' = H or N-hydroxysuccinimide;
e = 1 or 2 and
Z = imidazole.

The nitric monoxide metabolite is a low molecular weight S-nitroso-thiol compound, especially S-nitrosoglutathione.

ABEX

EXAMPLE - A mixture of polyethylene glycol 6000 (85 g), toluene (100 ml) and sodium acetate (0.2 g) was heated to 80degreesC to give a solution and then to reflux for 1 hour with removal of water. Succinic anhydride (2.4 g) was added and the mixture was stirred at 105degreesC for 3 hours and concentrated. The residue was cooled to 80degreesC and filtered to give 78 g of polyethylene glycol disuccinate.

The above compound (17.4g) and DMF (200 ml) were heated to 40degreesC and dicyclohexylcarbodiimide (0.98 g) and N-hydroxysuccinimide (0.56 g) were added. The mixture was stirred for 12 hours and added dropwise to Et2O (1l). The product was collected by filtration to give 16.5 g of the activated ester of polyethylene glycol 6000.

Erythrocytes (100 ml) were suspended in 0.9% NaCl (100 ml) and washed (x4) at 4degreesC. A portion (60 ml) were haemolysed using water (180 ml) and the membrane components were removed with a 0.22 mum filter and centrifugation. The obtained haemoglobin (3.29 g) was dissolved in pH 8.6 0.1M phosphate buffer (1000 ml) and the activated ester of polyethylene glycol (4.54 g) was added. The mixture was stirred for 2 hours at 4degreesC and an oxygen partial pressure of 1 Torr to give a solution of the polyoxyethylene-haemoglobin complex. The above solution was treated with 1 mM EDTA and 0.5 mM DTPA and disodium hydrogen phosphate was added to give pH 8.6. S-nitrosoglutathione (85.7 mg) was added and the mixture was stirred at 4degreesC for 12 hours. The product was purified by ultrafiltration to remove polyethylene glycol derivatives and lyophilized to give 5.95 g of the complex.

L117 ANSWER 7 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 2000-096805 [08] WPIX
DNC C2000-028042
TI New hemoglobin construct-complexes binding in vivo for delivery of hepatocyte-modifying substance to hepatocytes.
DC B04 B07
IN ADAMSON, J G; MOORE, M S C; WODZINSKA, J M
PA (HEMO-N) HEMOSOL INC
CYC 86
PI WO 9956723 A2 19991111 (200008)* EN 51p A61K009-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
CA 2236344 A1 19991030 (200014) EN A61K047-48 <--
AU 9936960 A 19991123 (200016)
EP 1075280 A2 20010214 (200111) EN A61K047-48 <--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002513747 W 20020514 (200236) 49p C07K014-805 <--
ADT WO 9956723 A2 WO 1999-CA396 19990430; CA 2236344 A1 CA 1998-2236344 19980430; AU 9936960 A AU 1999-36960 19990430; EP 1075280 A2 EP 1999-919005 19990430, WO 1999-CA396 19990430; JP 2002513747 W WO 1999-CA396 19990430, JP 2000-546750 19990430
FDT AU 9936960 A Based on WO 9956723; EP 1075280 A2 Based on WO 9956723; JP 2002513747 W Based on WO 9956723
PRAI CA 1998-2236344 19980430
IC ICM A61K009-00; **A61K047-48; C07K014-805**
ICS A61K031-70; A61K038-16; A61K048-00; A61K049-00; A61K051-08; A61P001-16; A61P043-00
AB WO 9956723 A UPAB: 20000215
NOVELTY - New hemoglobin construct complex (I) comprises hemoglobin and hepatocyte modifying substance bound to hemoglobin. (I) binds in vivo to deliver hepatocyte-modifying substance to hepatocytes.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a hemoglobin construct complex comprising hemoglobin, hepatocyte-modifying substance bound to hemoglobin and haptoglobin bound to hemoglobin.

ACTIVITY - Antineoplastic; antiviral; antiinflammatory; antiparasitic; antimicrobial; antioxidant; hepatoprotective; cytoprotective.

USE - Used for treatment of hepatocytic disorders, diagnosis of hepatic disorders and treatment of metastatic cells carrying haptoglobin receptors in mammalian patients (claimed). (I) is used to deliver drugs, diagnostics and imaging compounds to the liver and to modulate or initiate activity of other therapeutic or diagnostic agents delivered by other methods for hepatocyte modification e.g. prodrugs, enzymes or genes coding for enzymes and requiring activation to cause effect. (I) is used to deliver antineoplastics (doxorubicin, daunorubicin, ricin, diphtheria toxin, diphtheria toxin A), antivirals (ara-AMP, trifluorothymidine, interferon, anti-sense oligonucleotides, ribavirin, cytarabin, acyclovir, didonosine (sic), vidarabine, adefovir, zalcitabine, lamivudine, fialvridine and other nucleoside analogs), antiinflammatories, antiparasitics, antimicrobials, antioxidants (glutathione SA 3443, S-adenosylmethionine, superoxide dismutase, catalase, alpha -tocopherol, vitamin C, deferoxamine, (+)-cianidanol-3, mannitol, tryptophan, pantetheine, pantotheinic acid, cystamine, cysteine, acetylcysteine, folinic acid, uridine monophosphate, zinc sulfate, schizandrin B, kopsinine), hepatoprotectives, cytoprotectives (S-adenosyl-L-methionine; prostaglandins E1, E2, I2 and analogs, colchicines and silymarin), fibrosis-affecting agents, nucleic acids, lipid metabolism agents (prostaglandins E1, E2, I2 and analogs, dimethyl prostaglandin E, misoprostol, enisoprost, prostacyclin PGI2 and its analog iloprost), anti-toxicants, proteins or enzymes, preferably genes coding for proteins of interest, especially putrescine or primaquine as well as calcium channel blockers (trifluoroperazine, verapamil, nifedipine and related dihydropyridine compounds, diltiazem), proteinase inhibitors, atrial natriuretic peptide, alpha 2-macrofetoprotein, synthetic linear terpenoid, cholestyramine, eta -aminocaproic acid, phenylmethylsulfonyl fluoride, pepstatin, glycyrrhizin, fructose 1,6-biphosphate and ursodeoxycholic acid.

(I) is also used to deliver diagnostic agents (radiolabeled lysine and putrescine, and fluorescent monodansyl cadaverine and fluorescein) and to treat or prevent hepatic fibrosis and other chronic liver disorders such as viral hepatitis and alcoholic or cryptogenic liver disease.

ADVANTAGE - (I) specifically targets hepatic cells in vivo, including metastases arising from primary hepatoma, which are normally difficult to identify and treat due to their systemic distribution and small size. (I) May exert beneficial effects on neighboring cells even if not heptocytes. (I) provides extended circulating half-life.

Two test articles were prepared from purified human hemoglobin A0 modified with tritium-labeled N-ethylmaleimide ((3H)-NEM-Hb): (3H)-NEM-Hb alone in Ringer's lactate or complexed to slight excess of rat haptoglobin in rat plasma. Three groups were analyzed: (1) normal rats receiving modified hemoglobin-haptoglobin complex in plasma; (2) normal rats receiving modified hemoglobin only (approximately twice binding capacity of rat) and (3) haptoglobin-depleted rats receiving modified hemoglobin only.

3 mg hemoglobin was administered to conscious Sprague-Dawley rats in each case. Liver and plasma samples were collected at 30, 60 and 120 minutes post-administration and radioactivity counted after solubilization and quenching. Values were converted to percentages of total dose and concentration/dose.

Plasma retention was highest in (1) and both (1) and (2) were higher than (3). The greatest difference was seen at 130 minutes at which time (1) contained three times the radioactivity of (3) and 3.5 times that of (2). Liver content in (1) and (2) was higher than in (3) at all time points. At 30 minutes, (1) and (2) had approximately 20% of total dose in

liver compared with 11% in (3). Liver content was the same at 30 and 60 minutes in (1) and (2) and declined by the 120-minute point. By 120 minutes, (1) and (2) liver contents were 5- and 3-fold higher than (3), respectively. (1) and (2) contained 60% of dose in plasma and liver compartments at 30 minutes, compared with half that amount in (3). Liver to plasma concentration/dose ratios increased with time in all groups, with liver concentration four times that of plasma in (1) and (2) by 120 minutes, twice that of (3) at the same time.

The results demonstrate improvement in plasma retention and liver targeting with the modified hemoglobin.

Dwg.0/17

FS CPI

FA AB; DCN

MC CPI: B01-D01; B03-H; B04-B03C; B04-B04D2; B04-E01; B04-H03; B04-H05; B04-L01; B04-N04; B05-A03A; B05-B01G; B06-A01; B06-D02; B06-D04; B06-D09; B06-D18; B06-F01; B07-A02; B07-C; B07-D04C; B10-A07; B10-A15; B10-A22; B10-B01B; B10-B02; B10-C03; B10-D03; B10-G02; B12-K04; B14-A01; B14-A02; B14-B02; B14-C03; B14-H01; B14-N12; B14-S08

TECH UPTX: 20000215

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred complex: Hepatocyte-modifying substance is bound to hemoglobin through a chemical linker. Hepatocyte-modifying substance comprises an agent interacting with hepatocytes and acting in vivo at the liver and comprising therapeutic agents, diagnostic agents or markers. Hepatocyte modifying substance comprising a therapeutic agent comprising antineoplastics, antivirals, antiinflammatories, antiparasitics, antimicrobials, antioxidants, hepatoprotectives, cytoprotectives, fibrosis-affecting agents, nucleic acids, lipid metabolism agents, anti-toxicants, proteins or enzymes, preferably genes coding for proteins of interest, especially putrescine or primaquine. Hepatocyte-modifying substance comprises a diagnostic agent comprising radiolabeled compound or fluorescent compound.

Preferred hemoglobin: Hemoglobin comprises intramolecularly crosslinked human hemoglobin, preferably linked with crosslinking agent that leaves residual chemical groups available for subsequent reaction with hepatocyte-modifying agent either directly or through a chemical linker group, preferably trifunctional reagent that uses two of its functional groups for intramolecular crosslinking of hemoglobin and leaves its 3rd functional group available for reaction with a nucleophile, especially trimesoyl tris(3,5-dibromosalicylate).

L117 ANSWER 8 OF 16 WPIX (C) 2002 THOMSON DERWENT

AN 1999-591183 [50] WPIX

DNC C1999-172643

TI New conjugate of hemoglobin and a polysaccharide useful as an oxygen transporter.

DC A96 B04

IN ADAMSON, J G; ADAMSON, G W; ADAMSON, G

PA (HEMO-N) HEMOSOL INC; (ADAM-I) ADAMSON G

CYC 85

PI WO 9949897 A1 19991007 (199950)* EN 48p A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
CA 2233725 A1 19990930 (200009) EN A61K047-48 <--
AU 9929180 A 19991018 (200010)
EP 1066057 A1 20010110 (200103) EN A61K047-48 <--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
CN 1301179 A 20010627 (200158) A61K047-48 <--
JP 2002509898 W 20020402 (200225) 43p C07K014-805 <--

US 2002040128 A1 20020404 (200227) A61K038-00

ADT WO 9949897 A1 WO 1999-CA260 19990325; CA 2233725 A1 CA 1998-2233725 19980331; AU 9929180 A AU 1999-29180 19990325; EP 1066057 A1 EP 1999-910061 19990325, WO 1999-CA260 19990325; CN 1301179 A CN 1999-806176 19990325; JP 2002509898 W WO 1999-CA260 19990325, JP 2000-540859 19990325; US 2002040128 A1 US 1999-276686 19990326

FDT AU 9929180 A Based on WO 9949897; EP 1066057 A1 Based on WO 9949897; JP 2002509898 W Based on WO 9949897

PRAI CA 1998-2233725 19980331

IC ICM A61K038-00; **A61K047-48**; **C07K014-805**
ICS A61K035-14; A61K038-16; **A61K038-42**; A61K039-385; A61P007-08; C07K001-00; C07K014-00; C07K016-00; C07K017-00; C08B031-00

AB WO 9949897 A UPAB: 19991201
NOVELTY - A new conjugate of hemoglobin and a polysaccharide having a molecular weight of at least 70 kDa

DETAILED DESCRIPTION - New polysaccharide-hemoglobin conjugate useful as an oxygen transporter, comprises hemoglobin covalently linked through secondary amine linkages between amino groups on the hemoglobin and residues of aldehyde groups on the polysaccharide produced by oxidative saccharide ring opening, where the secondary amine linkages are formed by reaction of the amino groups and aldehyde groups in a stage to form Schiff base linkages, followed by a subsequent reduction to effect stabilization, and the conjugate has no detectable residual unbound hemoglobin and components of molecular weight higher than 500 kDa.

An INDEPENDENT CLAIM is also included for a process of preparing a hemoglobin based oxygen carrier.

USE - The oxygen carriers are useful for administration to patients as a supplement for or partial replacement for whole blood.

Dwg.0/12

FS CPI

FA AB; DCN

MC CPI: A12-V03B; B04-B04D2; B04-C02B; B04-C02C; B14-F11

TECH UPTX: 19991201
TECHNOLOGY FOCUS - BIOLOGY - Preferred components: The polysaccharide is hydroxyethyl starch of molecular weight 70-1000 kDa, with a substitution ratio of 0.5-0.7 and having a P50 of 4-50 at 37 degreesC. The hemoglobin is human hemoglobin, preferably deoxyhemoglobin and preferably intramolecularly cross-linked.

Preparation: The hemoglobin based oxygen carrier is prepared by reacting an oxidatively ring-opened polysaccharide carrying aldehyde groups with hemoglobin to form a conjugate, maintaining the conjugate under controlled conditions of aqueous solution with predetermined pH to effect controlled molecular weight reduction and molecular weight re-distribution of the conjugate to predetermined ranges of values, stabilizing the conjugate after the predetermined ranges of values have been achieved by reduction of the Schiff base linkages between the polysaccharide and the hemoglobin to stable secondary amine linkages and recovering a solution of the polysaccharide-hemoglobin so formed which contains no detectable product residue of molecular weight greater than 500-600 kDa. The conjugate is maintained in aqueous solution at pH about 7.2-10 and at about 15-30 degreesC to effect molecular weight reduction and molecular weight redistribution. The process includes a single stage of reduction to effect the stabilization and to reduce the residual aldehyde groups, the reduction being effected with a boron-based reducing agent, preferably borane dimethylamine, or includes two successive stages of reduction, the first to effect the stabilization and the second to reduce residual aldehyde groups.

Preferred product: The hydroxyethyl starch-hemoglobin conjugate has a molecular weight distribution of 100-200 kDa.

ABEX
EXAMPLE - Hydroxyethyl starch (HES) (9.0 g) with a weight average molecular weight of 450 kDa, having a degree of hydroxyethyl substitution

of 0.7, was dissolved in water (90 ml) and sodium meta-periodate (1.96 g) was added to an aliquot (30 ml) of this solution to provide 100% oxidation of the available diol groups. After 4 hours reaction in the dark at 4 degreesC, the solution was dialyzed extensively against chilled water and the final retentate was lyophilized to a white powder. Oxidized 450 kDa HES (0.54 g) was dissolved in 100 mM HEPES buffer pH 8.1 (3.0 ml) and the solution was added to carbonmonoxylated hemoglobin (COHb, 200 mg/ml in water) to give final Hb concentrations of approximately 10, 20 and 50 mg/ml respectively.

L117 ANSWER 9 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 1998-467160 [40] WPIX
DNN N1998-363982 DNC C1998-141579
TI Haemoglobin(s) modified with S-nitroso groups, and related compounds - used in treatment of e.g. ischaemic injury, hypertension, angina, reperfusion injury or inflammation.
DC B04 S03
IN GOW, A J; STAMLER, J S
PA (UYDU-N) UNIV DUKE MEDICAL CENT
CYC 22
PI WO 9834955 A1 19980813 (199840)* EN 167p C07K014-805 <--
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9861502 A 19980826 (199902) C07K014-805 <--
EP 1015490 A1 20000705 (200035) EN C07K014-805 <--
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002513400 W 20020508 (200234) 142p C07K014-805 <--
ADT WO 9834955 A1 WO 1998-US2383 19980205; AU 9861502 A AU 1998-61502 19980205; EP 1015490 A1 EP 1998-906222 19980205, WO 1998-US2383 19980205; JP 2002513400 W JP 1998-534943 19980205, WO 1998-US2383 19980205
FDT AU 9861502 A Based on WO 9834955; EP 1015490 A1 Based on WO 9834955; JP 2002513400 W Based on WO 9834955
PRAI US 1997-874992 19970612; US 1997-796164 19970206
IC ICM **C07K014-805**
ICS A61K038-16; **A61K038-42**; **A61K047-48**; A61P007-02; A61P009-10; A61P009-12; A61P009-14; G01N021-78; G01N033-49; G01N033-72
AB WO 9834955 A UPAB: 19981008
Treatment or prevention of diseases or medical disorders, which can be ameliorated by delivery of NO (or its biological equivalent) to tissues affected by the disease or disorder (in humans or animals), comprises administering: (i) nitrosyl-heme-containing donors of NO, (ii) a heme-based blood substitute and inhaled NO, (iii) CO-derivatised haemoglobin (Hb) and a nitrosated Hb; or (iv) Hb beta -chains.

Also claimed are: (1) a method for delivering CO to tissues in animals or humans, comprising administering CO-derivatised Hb; (2) a method for treating shock in humans or animals, comprising administering Hb alpha -chains; (3) a method for measuring NO equivalents in S-nitrosohaemoglobin (SNH) and nitrosyl-Fe(II)-Hb (NFH) in blood comprising red blood cells (RBCs), comprising: (a) lysing the RBCs of a blood sample; (b) preparing a desalted protein fraction of the lysed RBCs; (c) subjecting the fraction to photolysis, thus liberating NO from SNH and NFH; and (d) quantitating the NO in the fraction by measuring a chemiluminescence signal generated by a chemical reaction between NO and ozone, thus measuring NO equivalents in SNH and NFH; (4) a method for assaying NO production in disease states, comprising: (a) lysing the RBCs of a blood sample; (b) preparing a protein fraction of the lysed RBCs; (c) subjecting the fraction to photolysis, thus liberating NO from SNH and NFH; and (d) quantitating the NO in the fraction by measuring a chemiluminescence signal generated by a chemical reaction between NO and ozone; (5) a method for assaying NO equivalents in SNH and NFH in purified Hb, comprising measuring NO equivalents in the purified Hb by photolysis-chemiluminescence; (6) a method for measuring NO production in

SNH and NFH in RBCs, comprising: (a) isolating washed RBCS from blood and lysing the RBCs to give a lysate; (b) desalting the lysate; and (c) measuring NO equivalents in the lysate by photolysis-chemiluminescence; (7) a method for measuring NO bound to NFH in RBCs, comprising: (a) making a protein fraction from the RBCs; (b) treating the protein fraction with HgCl2 followed by exposure to air; and (c) subjecting the protein fraction to photolysis of the NO ligand of NFH followed by detection of NO by chemiluminescence; (8) a method for assaying SNH, comprising: (a) isolating RBCs from blood and lysing the RBCs to give a lysate; (b) desalting the lysate; (c) contacting an aliquot of the lysate with mercury ions in excess of protein concentration, thus obtaining a mercury-treated aliquot and an untreated aliquot; (d) exposing the treated and untreated aliquots to oxygen; (e) measuring NO equivalents in the aliquots by photolysis-chemiluminescence; and (f) determining a quantity of SNH from the NO equivalents measured in (e); (9) a method for assaying thiol-bound NO in SNH in RBCs, comprising: (a) isolating washed RBCs from blood; (b) lysing the RBCs to give a lysate; (c) desalting the lysate; (d) dividing the lysate into (i) an aliquot contacted with mercury ions in excess of the protein concentration of the lysate and (ii) an aliquot which is untreated with mercury; (e) exposing both aliquots to oxygen; (f) isolating a mercury-treated low molecular weight fraction and an untreated low molecular weight fraction from the aliquots; (g) contacting the low molecular weight fractions with excess low molecular weight thiol under acidic conditions, thus producing S-nitrosothiol; (h) measuring NO liberated from S-nitrosothiol in the fractions of (g) by photolysis-chemiluminescence; and (i) determining a quantity of thiol-bound NO in SNH from a difference in measurements in (h); (10) a method for measuring SNH and NFH in RBCs, comprising: (a) isolating washed RBCs from blood; (b) lysing the RBCs; (c) desalting the lysate; and (d) measuring NO equivalents from the lysate by photolysis-chemiluminescence; (11) a method for making stable nitrosyl-deoxyhaemoglobin, comprising adding NO to deoxyhaemoglobin in an aqueous solution such that the ratio of NO to heme is below 1:100 or more than 0.75; (12) a method for making SNO-oxyhaemoglobin, comprising adding NO to an aqueous solution of oxyhaemoglobin and a buffer with a pK of at least 9.4, at a concentration of 10-200 mM, at pH 7.4; (13) a method for making nitrosyl-oxyhaemoglobin, comprising adding NO to oxyhaemoglobin in an aqueous solution such that the ratio of NO to Hb is below 1:30; (14) Hb conjugated to an NO-donor; (15) a composition comprising Hb and one or more NO donors; (16) nitrosylhaemoglobin conjugated to one or more electron acceptors; (17) a composition comprising nitrosylhaemoglobin and one or more electron acceptors; (18) Hb conjugated to nitric oxide synthase; (19) a composition comprising Hb and nitric oxide synthase; (20) isolated erythrocytes comprising nitrosylhaemoglobin; (21) a method for making isolated erythrocytes comprising nitrosylhaemoglobin comprises incubating deoxygenated erthrocytes in a solution comprising NO; (22) a method for assaying SNH comprising (a)-(c) as in (9) followed by: (d) contacting an aliquot of the lysate of (c) with mercury ions in excess over protein concentration , to obtain a mercury-treated aliquot and an untreated aliquot; (e) exposing the mercury treated aliquot and the untreated aliquot to oxygen; (f) measuring NO equivalents in the two aliquots by photolysis chemoluminescence; (g) determining the quantity of SNH from the NO equivalents measured in (f); (23) a method for measuring SNH and NFH in a sample comprising (a)-(c) as in (9) followed by the step of measuring NO equivalents in the lysate by photolysis-chemoluminescence; (24) a method for assaying NFH comprising (a)-(f) as in (22) where step (f) gives information about SNH and NFH + SNH concentration NFH concentration is assayed by subtracting SNH concentration form the figure for NFH = SNH concentration.

USE - The inventions can be used for producing and isolating S-nitrosohaemoglobin ((SNO-Hb) e.g. for use in therapy) by reaction of Hb with S-nitrosothiol in procedures which avoid oxidation of the heme. The methods can also be used for producing isolated, nitrosated and nitrated

derivatives of Hbs in which the heme iron may or may not be oxidised. The methods can also be used as methods of therapy for conditions requiring oxidation, scavenging of free radicals, or release of NO+ groups to tissues, involving administration of compositions comprising SNO-Hb, thiols and/or NO-donating agents. Examples of such conditions incude ischaemic injury, hypertension, angina, reperfusion injury, inflammation or diseases characterised by thrombosis.
Dwg.0/26

FS CPI EPI
FA AB; DCN
MC CPI: B04-B04D2; B14-C03; B14-F01D; B14-F02B; B14-F02D; B14-F05
EPI: S03-E14H

L117 ANSWER 10 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 1998-078023 [08] WPIX
DNC C1998-026137
TI Oxygen transporter containing haemoglobin-hydroxyethyl starch conjugate - used as a blood additive, plasma expander, perfusion agent, haemo-dilution agent and/or cardioplegic solution.
DC A11 A96 B04
IN EICHNER, W; SOMMERMEYER, K
PA (FREP) FRESENIUS AG
CYC 24
PI DE 19628705 A1 19980115 (199808)* 7p A61K038-42 <--
WO 9801158 A2 19980115 (199809) DE 25p A61K047-48 <--
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU BR CA JP MX US
AU 9735411 A 19980202 (199826) A61K047-48 <--
EP 912197 A2 19990506 (199922) DE A61K047-48 <--
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
AU 710879 B 19990930 (199952) A61K047-48 <--
BR 9710865 A 20000111 (200020) A61K047-48 <--
US 6083909 A 20000704 (200036) A61K038-42 <--
JP 2000514434 W 20001031 (200059) 23p A61K038-16
MX 9900402 A1 20000101 (200115) A61K047-48 <--
EP 912197 B1 20011205 (200203) DE A61K047-48 <--
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
DE 59705678 G 20020117 (200206) A61K047-48 <--
ES 2166551 T3 20020416 (200230) A61K047-48 <--
MX 204161 B 20010910 (200239) A61K047-48 <--
ADT DE 19628705 A1 DE 1996-19628705 19960708; WO 9801158 A2 WO 1997-EP3527 19970707; AU 9735411 A AU 1997-35411 19970707; EP 912197 A2 EP 1997-931768 19970707, WO 1997-EP3527 19970707; AU 710879 B AU 1997-35411 19970707; BR 9710865 A BR 1997-10865 19970707, WO 1997-EP3527 19970707; US 6083909 A WO 1997-EP3527 19970707, US 1999-214430 19990106; JP 2000514434 W WO 1997-EP3527 19970707, JP 1998-504767 19970707; MX 9900402 A1 MX 1999-402 19990108; EP 912197 B1 EP 1997-931768 19970707, WO 1997-EP3527 19970707; DE 59705678 G DE 1997-505678 19970707, EP 1997-931768 19970707, WO 1997-EP3527 19970707; ES 2166551 T3 EP 1997-931768 19970707; MX 204161 B MX 1999-402 19990108
FDT AU 9735411 A Based on WO 9801158; EP 912197 A2 Based on WO 9801158; AU 710879 B Previous Publ. AU 9735411, Based on WO 9801158; BR 9710865 A Based on WO 9801158; US 6083909 A Based on WO 9801158; JP 2000514434 W Based on WO 9801158; EP 912197 B1 Based on WO 9801158; DE 59705678 G Based on EP 912197, Based on WO 9801158; ES 2166551 T3 Based on EP 912197
PRAI DE 1996-19628705 19960708
IC ICM A61K038-16; **A61K038-42**; **A61K047-48**
ICS A61K038-00; A61K038-38; A61P007-08; **C07K014-805**; C08B031-18
AB DE 19628705 A UPAB: 19980223
Oxygen transport agent contains a haemoglobin-hydroxyethyl starch conjugate with selective amide bonding between free amino groups of the haemoglobin and the oxidised form of reduced end-groups of hydroxyethyl starch.

USE - The transport agent is used as a blood additive, plasma expander, perfusion agent, haemo-dilution agent and/or cardioplegic solution.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: A03-A00A; A12-V01; B04-B04D2; B04-C02B; B04-N02; B14-F05; B14-F11

L117 ANSWER 11 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 1996-454963 [45] WPIX
CR 1995-098723 [13]; 1998-249873 [22]; 1998-260553 [23]; 1998-505692 [43]; 1998-520171 [44]; 1998-556430 [47]; 1998-582624 [49]
DNC C1996-142573
TI Compsns. and processes for, e.g. alleviating free radical toxicity - using nitroxide cpd. in association with macromolecules such as albumin or haemoglobin.
DC B03 B04 P31
IN HSIA, J
PA (SYNZ-N) SYNZYME TECHNOLOGIES INC; (HSIA-I) HSIA J
CYC 30
PI WO 9629974 A2 19961003 (199645)* EN A61K000-00
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA CN JP KP KR MX NZ RU SG US
AU 9666351 A 19961016 (199706) A61K038-00
WO 9629974 A3 19970327 (199729) A61K000-00
EP 817628 A1 19980114 (199807) EN A61K031-40
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 5767089 A 19980616 (199831) A61B005-055
US 5840701 A 19981124 (199903) A61K031-04
JP 11502846 W 19990309 (199920) 154p A61K009-00
KR 98703427 A 19981105 (199954) A61K031-785
MX 9707513 A1 19980301 (200002) A61K000-00
AU 714661 B 20000106 (200013) A61K038-00
NZ 313806 A 20010629 (200140) A61K047-48 <--
US 2002013263 A1 20020131 (200210) A61K038-42 <--
ADT WO 9629974 A2 WO 1996-US3644 19960329; AU 9666351 A AU 1996-66351 19960329; WO 9629974 A3 WO 1996-US3644 19960329; EP 817628 A1 EP 1996-926048 19960329, WO 1996-US3644 19960329; US 5767089 A CIP of US 1993-107543 19930816, CIP of US 1994-291590 19940815, US 1995-417132 19950331; US 5840701 A CIP of US 1993-107543 19930816, CIP of US 1994-291590 19940815, CIP of US 1995-417132 19950331, CIP of US 1995-482952 19950607, US 1996-605531 19960222; JP 11502846 W JP 1996-529473 19960329, WO 1996-US3644 19960329; KR 98703427 A WO 1996-US3644 19960329, KR 1997-706831 19970929; MX 9707513 A1 MX 1997-7513 19970929; AU 714661 B AU 1996-66351 19960329; NZ 313806 A NZ 1996-313806 19960329, WO 1996-US3644 19960329; US 2002013263 A1 CIP of US 1993-107543 19930816, CIP of US 1994-291590 19940815, CIP of US 1995-417132 19950331, CIP of US 1995-482952 19950607, CIP of US 1996-605531 19960222, Cont of US 1997-824739 19970326, US 2001-894237 20010627
FDT AU 9666351 A Based on WO 9629974; EP 817628 A1 Based on WO 9629974; US 5840701 A CIP of US 5591710; JP 11502846 W Based on WO 9629974; KR 98703427 A Based on WO 9629974; AU 714661 B Previous Publ. AU 9666351, Based on WO 9629974; NZ 313806 A Div in NZ 510860, Based on WO 9629974; US 2002013263 A1 CIP of US 5591710, CIP of US 5767089, CIP of US 5840701
PRAI US 1996-605531 19960222; US 1995-417132 19950331; US 1995-482952 19950607; US 1993-107543 19930816; US 1994-291590 19940815
REP 1.Jnl.Ref; US 4863717; US 5407657; WO 9113619; WO 9505397
IC ICM A61B005-055; A61K000-00; A61K009-00; A61K031-04; A61K031-40; A61K031-785; A61K038-00; **A61K038-42**; **A61K047-48**
ICS A61K009-127; A61K031-715; A61K031-721; A61K031-724; A61K035-18; A61K038-16; A61K038-38; A61K045-06; A61K049-00; A61K051-06
ICA C07D207-46; C07D209-42; C07D211-94
AB WO 9629974 A UPAB: 20020213

The following are claimed: (A) promoting in vivo conversion of a hydroxylamine form of a nitroxide to a paramagnetic form, comprising: reacting a first nitroxide in the hydroxylamine form with a second nitroxide providing enzyme-mimic activity as a hydroxylamine oxidase, the enzyme mimic cpd. being a nitroxide cpd. having a nitroxyl gp. which is less stable than the first nitroxide in its free radical form. (B) providing a localised increase in the in vivo concn. of the free radical form of a nitroxide, comprising: (a) administering a membrane-permeable first nitroxide (MP1N); and (b) administering a localised dose of a second nitroxide having a nitroxyl gp. capable of accepting an electron from the hydroxylamine form of the first nitroxide. (C) compsn. comprising a polynitroxide macromolecule (PM) in a vehicle for admin. (D) compsn. comprising: (a) a MP1N; and (b) a second nitroxide having a nitroxyl gp. capable of accepting an electron from the first nitroxide (this type of cpd. is denoted 2NX). (E) enhancing the electron paramagnetic resonance or nuclear magnetic resonance image of a biological structure, comprising: (a) administering a MP1N; (b) administering a 2NX; and (c) obtaining an image of the biological structure, (F) obtaining an EPR or MRI image of ischaemia in the heart or brain, comprising intravenous admin. of a membrane-impermeable PM. (G) alleviating ischaemic reperfusion injury comprising admin. of a PM. (H) protecting an organism from ionising radiation, comprising: (a) admin. of a MP1N; and (b) admin. of a membrane-impermeable 2NX. (I) treatment of organisms with a physiological condition using a therapeutic dose of ionising radiation, comprising: (a) admin. of a MP1N; (b) admin. of a 2NX; and (c) exposing the organism to ionising radiation. (J) reducing the effect of free radical toxicity in biological systems, comprising: (a) admin. of a MP1N; and (b) admin. of a catalytic amt. of a 2NX.

USE - The therapeutic processes described above may be used for treatment of e.g. oxidative stress and biological damage associated with free radical toxicity, inflammation, radiation, head injury, shock, post-ischaemic reperfusion injury, stroke, renal failure, endothelial damage, lipid peroxidation, sickle cell anaemia, leukocyte activation and aggregation, apoptosis, ionising radiation, alopecia, cataracts, sepsis, psoriasis, ulcers and the ageing process. The polynitroxide macromolecules may be used as blood substitutes, imaging agents, radioprotective agents or therapeutic agents. Admin. is e.g. oral, rectal or parenteral.

FS CPI GMPI
FA AB; DCN
MC CPI: B04-B04D2; B05-C03; B11-C08; B12-K04A; B12-K07; B14-M01; B14-S08

L117 ANSWER 12 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 1996-363016 [37] WPIX
DNC C1996-114399
TI Haemoglobin crosslinked to superoxidedismutase and catalase - used as blood substitute with reduced ischaemic-reperfusion risks.
DC B04 D16 D22
IN CHANG, T M S; DAGNILLO, F; D'AGNILLO, F
PA (DAGN-I) D'AGNILLO F; (UYMC-N) UNIV MCGILL ROYAL INST ADVANCEMENT; (CHAN-I) CHANG T M S
CYC 2
PI CA 2135739 A 19960515 (199637)* 17p C12N009-08
US 5606025 A 19970225 (199714)# 6p A61K038-42 <--
CA 2135739 C 19971021 (199803) C12N009-08
ADT CA 2135739 A CA 1994-2135739 19941114; US 5606025 A US 1994-341873 19941115; CA 2135739 C CA 1994-2135739 19941114
PRAI CA 1994-2135739 19941114; US 1994-341873 19941115
IC ICM **A61K038-42**; C12N009-08
ICS A61K035-14; A61K037-50; A61K038-44; A61K038-54; **A61K047-48**; **C07K014-805**; C12N009-02; C12N011-02
AB CA 2135739 A UPAB: 19970313
A complex comprises intramolecularly and/or intermolecularly crosslinked haemoglobin and at least 1 endogenous enzyme chemically bonded to it, the

enzyme being either or both of superoxide dismutase (SOD) and catalase; the complex having a mol. wt. of at least 54 kDa. Also claimed is a method of preparing the complex.

The complex has both SOD and catalase bonded to haemoglobin with a crosslinking agent, selected from glutaraldehyde, diaspirin derivs., polyaldehydes derived from oxidative ring-opening of oligosaccharides, and di- and triphosphate esters. The enzymes are in amt. 0.1-10 (pref. 0.5-2.5)% by wt., and the ratio of SOD to catalase is from 1:1 to 5:1 (pref. 1.5:1 to 2.5:1). The method comprises reacting an aq. soln. of purified uncrosslinked haemoglobin (Hb) with SOD and catalase and a haemoglobin crosslinking agent. The reaction is quenched with a reagent which reacts with the crosslinking agent and the PolyHb-SOD-catalase crosslinked complex is recovered.

USE - The complex is useful (claimed) as an oxygen transporting rescusitative fluid which can be used as a blood substitute. It can also be used in the preservation of donor organs.

ADVANTAGE - The enzymes scavenge superoxide and hydrogen peroxide, preventing the formation of free radicals which can cause reperfusion injury in ischaemic tissues or organs.

Dwg.0/0

FS CPI
FA AB
MC CPI: B04-B04D2; B04-L03; B14-F02D; B14-F05; D05-A01A4; D05-A01B1; D09-A01
ABEQ US 5606025 A UPAB: 19970407

A complex of intramolecularly and/or intermolecularly crosslinked haemoglobin, and endogenous enzymes chemically bonded to it, the endogenous enzymes being superoxide dismutase (SOD) and catalase, the molecular weight of the complex being at least 64 kilodaltons, the oxygen-carrying crosslinked haemoglobin component of the complex comprising about 90-99.9% by weight of it and the total weight of bound enzymes in the complex comprising about 0.1-10% by weight of it.

Dwg.0/4

L117 ANSWER 13 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 1995-336940 [43] WPIX
CR 1991-177872 [24]; 1994-151239 [18]; 1997-384695 [35]
DNC C1995-148581
TI Enhancement of antitumour therapy - by using radiation or chemotherapy in combination with haemoglobin conjugated to non-antigenic polymer.
DC A96 B04
IN NHO, K
PA (ENZO-N) ENZON INC
CYC 64
PI WO 9525121 A1 19950921 (199543)* EN 21p C07K014-00
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG UZ VN
AU 9521878 A 19951003 (199602)
US 5478806 A 19951226 (199606) 8p C07K014-805 <--
EP 750633 A1 19970102 (199706) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
US 5658879 A 19970819 (199739) 9p A61K038-42 <--
JP 09509966 W 19971007 (199750) 21p A61K038-16
AU 682766 B 19971016 (199801) C07K014-00
ADT WO 9525121 A1 WO 1995-US3462 19950315; AU 9521878 A AU 1995-21878 19950315; US 5478806 A Cont of US 1989-440553 19891122, CIP of US 1992-888039 19920522, CIP of US 1992-960007 19921013, US 1994-213881 19940316; EP 750633 A1 EP 1995-914763 19950315, WO 1995-US3462 19950315; US 5658879 A Cont of US 1989-440553 19891122, CIP of US 1992-888039 19920522, CIP of US 1992-960007 19921013, Cont of US 1994-213881 19940316, US 1995-543386 19951016; JP 09509966 W JP 1995-524219 19950315, WO 1995-US3462 19950315; AU 682766 B AU 1995-21878 19950315

FDT AU 9521878 A Based on WO 9525121; US 5478806 A CIP of US 5312808, CIP of US 5386014; EP 750633 A1 Based on WO 9525121; US 5658879 A CIP of US 5312808, CIP of US 5386014, Cont of US 5478806; JP 09509966 W Based on WO 9525121; AU 682766 B Previous Publ. AU 9521878, Based on WO 9525121
PRAI US 1994-213881 19940316; US 1989-440553 19891122; US 1992-888039 19920522; US 1992-960007 19921013; US 1995-543386 19951016
REP US 5234903; US 5264555; US 5312808; US 5386014
IC A61K038-16; **A61K038-42**; C07K014-47; **C07K014-805**
ICM A61K038-16; **A61K038-42**; C07K014-00; **C07K014-805**
ICS **A61K047-48**; A61N005-00; C07K014-47; C07K017-08; C07K017-10
AB WO 9525121 A UPAB: 19970926
Enhancing the effectiveness of antitumour therapy in mammals comprises administering radiation in combination with haemoglobin (Hb) conjugated to a non-antigenic polymer.

Also claimed is a method of reducing tumour burden in mammals comprising administering an antitumour therapy selected from radiation and/or a chemotherapeutic agent in combination with Hb conjugated to a non-antigenic polymer.

ADVANTAGE - Hb-polymer conjugates preferentially localise in hypoxic areas including tumour lesions. They synergistically enhance radiation and/or chemotherapy by providing high levels of oxygen locally. The conjugates can be used in amts. of e.g. 0.24-6.3, pref. 0.72-2 g/kg by e.g. i.v. infusion or transfusion.

Dwg.2/4
FS CPI
FA AB; GI; DCN
MC CPI: A12-V03; B04-B04D2; B04-C02; B04-C03; B05-C08; B14-H01B; B14-S09
ABEQ US 5478806 A UPAB: 19960212
A method of enhancing the effectiveness of antitumour therapy in mammals, comprising:

administering to a mammal in need of such therapy an effective amount of radiation in combination with haemoglobin covalently conjugated to a poly(alkylene oxide), said haemoglobin conjugate being present in an amount sufficient to enhance the effectiveness of said radiation.

Dwg.0/4
ABEQ US 5658879 A UPAB: 19970926
A method of reducing tumour burden in mammals, comprising administering to a mammal in need such therapy an effective amount of:

(a) an anti-tumour therapy comprising a chemotherapeutic agent in combination with

(b) haemoglobin covalently conjugated to a polyalkylene oxide, said haemoglobin conjugate being present in a amount sufficient to enhance the effectiveness of said anti-tumour therapy.

Dwg.0/0

L117 ANSWER 14 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 1994-151239 [18] WPIX
CR 1991-177872 [24]; 1995-336940 [43]; 1997-384695 [35]
DNC C1994-069545
TI New poly alkylene oxide conjugated haemoglobin solns. - contain conjugate(s) with high mol. wt. and high degree of substitution to eliminate haemoglobinuria when used in mammals.
DC A96 B04
IN CHO, M; NHO, K; SHORR, R G L; CHO, M P
PA (ENZO-N) ENZON INC
CYC 33
PI WO 9409027 A1 19940428 (199418)* EN 30p C07K003-12
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU BR CA CZ FI HU JP KR NO NZ PL RO RU SE SK UA
US 5312808 A 19940517 (199419) 7p A61K037-00
AU 9346880 A 19940509 (199432)
EP 665850 A1 19950809 (199536) EN C07K003-12
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

US 5478805	A	19951226 (199606)	8p	A61K038-16
JP 08502023	W	19960305 (199644)	25p	A61K038-16
EP 665850	A4	19960724 (199701)		C07K003-12
NZ 254661	A	19970526 (199727)		A61K035-14
AU 678169	B	19970522 (199729)		C07K003-18

ADT WO 9409027 A1 WO 1993-US6972 19930726; US 5312808 A CIP of US 1989-440553 19891122, CIP of US 1990-616129 19901120, US 1992-960007 19921013; AU 9346880 A AU 1993-46880 19930726; EP 665850 A1 EP 1993-917336 19930726, WO 1993-US6972 19930726; US 5478805 A CIP of US 1989-440553 19891122, CIP of US 1990-619129 19901120, Cont of US 1992-960007 19921013, US 1993-146847 19931103; JP 08502023 W JP 1993-519670 19930726, WO 1993-US6972 19930726; EP 665850 A4 EP 1993-917336 ; NZ 254661 A NZ 1993-254661 19930726, WO 1993-US6972 19930726; AU 678169 B AU 1993-46880 19930726

FDT US 5312808 A CIP of US 5234903; AU 9346880 A Based on WO 9409027; EP 665850 A1 Based on WO 9409027; US 5478805 A CIP of US 5234903, Cont of US 5312808; JP 08502023 W Based on WO 9409027; NZ 254661 A Based on WO 9409027; AU 678169 B Previous Publ. AU 9346880, Based on WO 9409027

PRAI US 1992-960007 19921013; US 1989-440553 19891122; US 1990-616129 19901120; US 1990-619129 19901120; US 1993-146847 19931103

REP 2.Jnl.Ref; 4.Jnl.Ref; EP 206448; EP 67029; GB 2055868; WO 9107190; WO 9203153; WO 9208478

IC ICM A61K035-14; A61K037-00; A61K038-16; C07K003-12; C07K003-18
ICS A61K037-02; A61K037-14; **A61K047-48**; B01J041-04; C07K001-18; C07K003-22; **C07K014-805**; C07K017-08; C12N011-08

AB WO 9409027 A UPAB: 19970909

(A) a polyalkylene oxide (PAO)-conjugated haemoglobin (Hb)-contg. soln. is claimed comprising PAO-conjugated Hb having a mol. wt. greater than 85000 Daltons and a degree of substitution of at least 5 PAO conjugates per Hb molecule, where the soln. does not produce haemoglobinuria in mammals.

(B) Also claimed is a method of simultaneously fractionating and purifying PAO-Hb conjugates comprising (a) contacting PAO-Hb conjugates in soln. with an anion exchange medium capable of selectively binding (i) PAO-Hb conjugates having a mol. wt. of less than 85000 Daltons and a degree of substitution of less than 5 PAO conjugates per Hb molecule and (ii) physiologically unacceptable materials, so that fractions comprising conjugated Hbs having mol. wt. greater than 85000 Daltons and degrees of substitution greater than 5 PAO conjugates per Hb molecule are not bound by the medium, and (b) recovering the fractions comprising conjugated Hb not bound by the medium.

USE/ADVANTAGE - The Hb conjugates are used as alternatives to whole blood or blood fractions for use as oxygen carriers and plasma expanders. The conjugation of PAO to Hb reduces its antigenicity and extends its residence time in circulation. The use of the higher mol. wt. Hb conjugates eliminates the problem of haemoglobinuria caused by low mol. wt. conjugates. The purificn. method removes the low mol. wt. conjugates and also unacceptable materials such as DNA, endotoxins and phospholipids.

Dwg.0/0

FS CPI

FA AB

MC CPI: A05-H01; A10-E; A12-V02; B04-C03B; B11-B; B14-F11

ABEQ US 5312808 A UPAB: 19940627

Blood substitute comprises an aq. soln. of haemoglobin conjugated with a poly(alkylene oxide) and nontoxic buffer agent. The conjugate concn. is about 1-10 wt.% (pref. 4-6 wt.%) and the conjugate contains at least five polyethyleneglycol, polypropyleneglycol or corresp. block copolymer units per haemoglobin molecule, such that the conjugate has Mr more than 85000 (pref. 90000-120000).

USE/ADVANTAGE - The prods. are improved blood substitutes that avoid mammalian haemoglobinuria as a side effect. The blood substitutes avoid unfavourable immune responses or reactions, or contamination with bacteria or viruses e.g. HIV etc.

Dwg.0/0

ABEQ US 5478805 A UPAB: 19960212

A method of simultaneously fractionating and purifying polyalkylene oxide-haemoglobin (PAO-Hb) conjugates, comprising:

(a) loading a solution containing PAO-Hb conjugates onto an anion exchange medium capable of selectively binding

(i) PAO-Hb conjugates having a molecular weight of less than approximately 85,000 daltons and a degree of substitution of less than five polyalkylene oxide conjugates per haemoglobin molecule and

(ii) physiologically unacceptable materials selected from the group consisting of DNA, endotoxins and phospholipids; and

(b) recovering the PAO-Hb conjugates not bound by said resin.

Dwg.0/0

L117 ANSWER 15 OF 16 WPIX (C) 2002 THOMSON DERWENT
AN 1993-167403 [20] WPIX
CR 1990-361480 [48]; 1993-167626 [20]; 1997-052322 [05]
DNC C1993-074747
TI New conjugate of drug and haemoglobin or analogues - used for controlled release to blood, with better stability and longer half life, esp. for peptide(s) e.g. angiotensin.
DC B04 B07 C03 C07 P34
IN ANDERSON, D C; MATHEWS, A J; STETLER, G L; ANDERSEN, D C; HOFFMAN, S J; LOOKER, D L; NAGAI, K; ROSENDAHL, M S; WAGENBACH, M
PA (SOMA-N) SOMATOGEN INC
CYC 40

PI	WO 9308842	A1	19930513 (199320)*	EN 54p	A61K047-48	<--
	RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA SE					
	W: AT AU BB BG BR CA CH CS DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO PL RO RU SD SE UA US					
	AU 9331324	A	19930607 (199338)			
	EP 611306	A1	19940824 (199433)	EN		
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE					
	FI 9402138	A	19940629 (199433)		C07K000-00	
	JP 07500840	W	19950126 (199513)		A61K047-48	<--
	JP 07501059	W	19950202 (199514)		C07K014-805	<--
	AU 665599	B	19960111 (199609)		A61K047-42	
	US 5545727	A	19960813 (199638)	130p	C12N015-12	
	US 5679777	A	19971021 (199748)	42p	A61K035-14	
	US 5744329	A	19980428 (199824)	133p	C12P021-06	
	SG 47882	A1	19980417 (199827)		C07K015-00	
	US 5759517	A	19980602 (199829)		A61K051-00	
	EP 611306	B1	19980708 (199831)	EN		
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE					
	DE 69225978	E	19980723 (199835)		C07K014-00	
	EP 857489	A2	19980812 (199836)	EN		
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE					
	DE 69226197	E	19980813 (199838)			
	US 5798227	A	19980825 (199841)		C12P021-06	
	US 5801019	A	19980901 (199842)		C12P021-06	
	US 5844088	A	19981201 (199904)		C07K014-805	<--
	US 5844089	A	19981201 (199904)		C07K014-805	<--
	US 6274331	B1	20010814 (200148)		G01N033-53	

ADT WO 9308842 A1 WO 1992-US9713 19921106; AU 9331324 A AU 1993-31324 19921106; EP 611306 A1 EP 1992-925154 19921106, WO 1992-US9713 19921106; FI 9402138 A WO 1992-US9752 19921106, FI 1994-2138 19940509; JP 07500840 W WO 1992-US9713 19921106, JP 1993-508781 19921106; JP 07501059 W WO 1992-US9752 19921106, JP 1993-508788 19921106; AU 665599 B AU 1993-31324 19921106; US 5545727 A CIP of US 1989-349623 19890510, CIP of US 1989-374161 19890630, CIP of US 1989-379116 19890713, CIP of US 1991-671707 19910401, US 1991-789179 19911108; US 5679777 A CIP of US 1991-789177 19911108, CIP of US 1991-789179 19911108, WO 1992-US9713 19921106, US 1994-240711 19940712; US 5744329 A CIP of US 1989-349623 19890510, CIP of US 1989-374161 19890630, CIP of US 1989-379116 19890713, Div ex WO 1990-US2654 19900510, CIP of US 1991-671707 19910401, Div ex US

1991-789179 19911108, US 1995-444942 19950519; SG 47882 A1 SG 1996-4964 19921106; US 5759517 A CIP of US 1991-789177 19911108, CIP of US 1991-789179 19911108, Div ex WO 1992-US9713 19921106, Div ex US 1994-240711 19940712, US 1995-457753 19950601; EP 611306 B1 EP 1992-925154 19921106, WO 1992-US9713 19921106; DE 69225978 E DE 1992-625978 19921106, EP 1992-925173 19921106, WO 1992-US9752 19921106; EP 857489 A2 Div ex EP 1992-925173 19921106, EP 1997-203723 19921106; DE 69226197 E DE 1992-626197 19921106, EP 1992-925154 19921106, WO 1992-US9713 19921106; US 5798227 A CIP of US 1989-349623 19890510, CIP of US 1989-374161 19890630, CIP of US 1989-379116 19890713, Div ex WO 1990-US2654 19900510, CIP of US 1991-671707 19910401, Div ex US 1991-789179 19911108, US 1995-446105 19950519; US 5801019 A CIP of US 1989-349623 19890510, CIP of US 1989-374161 19890630, CIP of US 1989-379116 19890713, Div ex WO 1990-US2654 19900510, CIP of US 1991-671707 19910401, Div ex US 1991-789179 19911108, US 1995-444939 19950519; US 5844088 A CIP of US 1989-349623 19890510, CIP of US 1989-374161 19890630, CIP of US 1989-379116 19890713, Div ex WO 1990-US2654 19900510, CIP of US 1991-671707 19910401, Div ex US 1991-789179 19911108, US 1995-444991 19950519; US 5844089 A CIP of US 1989-349623 19890510, CIP of US 1989-374161 19890630, CIP of US 1989-379116 19890713, Div ex WO 1990-US2654 19900510, CIP of US 1991-671707 19910401, Div ex US 1991-789179 19911108, US 1995-450733 19950525; US 6274331 B1 CIP of US 1989-349623 19890510, CIP of US 1989-374161 19890630, CIP of US 1989-379116 19890713, CIP of WO 1990-US2654 19900510, CIP of US 1991-671707 19910401, Div ex US 1991-789179 19911108, US 1995-444915 19950519

FDT AU 9331324 A Based on WO 9308842; EP 611306 A1 Based on WO 9308842; JP 07500840 W Based on WO 9308842; JP 07501059 W Based on WO 9309143; AU 665599 B Previous Publ. AU 9331324, Based on WO 9308842; US 5679777 A CIP of US 5545727, Based on WO 9308842; US 5744329 A Div ex US 5545727; US 5759517 A CIP of US 5545727; EP 611306 B1 Based on WO 9308842; DE 69225978 E Based on EP 611376, Based on WO 9309143; EP 857489 A2 Div ex EP 611376; DE 69226197 E Based on EP 611306, Based on WO 9308842; US 5798227 A Div ex US 5545727; US 5801019 A Div ex US 5545727; US 5844088 A Div ex US 5545727; US 5844089 A Div ex US 5545727; US 6274331 B1 Div ex US 5545727

PRAI US 1991-789179 19911108; US 1991-789177 19911108; US 1989-349623 19890510; US 1989-374161 19890630; US 1989-379116 19890713; US 1991-671707 19910401; US 1994-240711 19940712; WO 1990-US2654 19900510; US 1995-444942 19950519; US 1995-457753 19950601; US 1995-446105 19950519; US 1995-444939 19950519; US 1995-444991 19950519; US 1995-450733 19950525; US 1995-444915 19950519

REP 2.Jnl.Ref; WO 9013645; WO 9108220; 6.Jnl.Ref; EP 290252; EP 402300; WO 8809179; WO 9116349; WO 9211283

IC ICM A61K035-14; A61K047-42; **A61K047-48**; A61K051-00; C07K000-00; C07K014-00; **C07K014-805**; C07K015-00; C12N015-12; C12P021-06; G01N033-53

ICS A61K038-16; A61K039-385; A61K049-02; A61M036-14; C07H017-00; C07K001-10; C12N001-20; C12N015-09; C12P021-04

AB WO 9308842 A UPAB: 20010829

New conjugate (A) of a drug (I), other than albumin, and a haemoglobin-like protein (II) can release active (I) under physiological conditions.

Pref. (I) is covalently bonded to (II), esp. directly or indirectly to a Cys residue. (II) may be a nutein of normal human haemoglobin with altered O2 affinity, increased intravascular retention or inhibited haptoglobin binding; or it is a pseudo oligomer with 2 or more globin-like domains which is asymmetrically mutated to provide a single additional crosslinkable Cys for attachment to (I).

The Cys residue to which (I) is attached is e.g. a mutation of a non-Cys residue in alpha or beta globin, or it may reside in the crevice in oxy or deoxy form. If attached via a disulphide, the Cys residue is in a region where approach of endogenous reduced agents is electrostatically or sterically hindered. Peptides drug may be derivatised to provide an SH

gp. for crosslinking to Cys and modified to improve disulphide bond stability. Also suitable as (I) are synthetic drugs; nucleic acids; polymers; herbicides or pesticides (for use on plants), etc.

(A) are incorporated into tablets, capsules, injectable solns. etc. and the dose is usually enough to provide a concn. in the blood of InM-ImM.

USE/ADVANTAGE - (A) are esp. used for controlled release into the blood of (I) with intravascular half life less than that of (II), partic. a peptide vasoconstrictive or vasodilating agent e.g. angiotensin II or atrial natriunetic factor. Conjugation to (II) stabilises (I); extends their half-like and improves retention in the blood stream. (A) may provide simultaneous release of (I) and O2 (some (I), e.g. antitumour agents, are more effective in presence of O2). The use of (A) as imaging agents, e.g. where (I) is 99m-Tc, is also contemplated.

Dwg.O/O

FS CPI GMPI

FA AB; DCN

MC CPI: B04-B04D2; B04-B04D3; B04-C01B; B12-F06; B12-F07

ABEQ US 5545727 A UPAB: 19960924

A DNA molecule comprising a DNA sequence coding on expression for non-naturally occurring, genetically fused, pseudodimeric di-alpha globin-like polypeptide consisting essentially of two and only two alpha globin-like domains, connected either directly by one peptide bond or by a peptide linker of 1-5 amino acids into a single unbranched polypeptide chain, said chain being capable of associating with beta globin and incorporating heme to form a pseudotetrameric hemoglobin-like protein with reversible oxygen binding activity.

Dwg.0/36

ABEQ US 5679777 A UPAB: 19971209

A conjugate of (a) a drug of interest, other than albumin, and (b) a hemoglobin-like protein,

where the conjugate (1) has a therapeutic activity, as a conjugate, which is attributable to said drug, and/or (2) is capable of releasing the drug in therapeutically active form under physiological conditions,

and where at least one of the following conditions applies:

(I) the hemoglobin-like protein is not identical to human hemoglobin AO or human hemoglobin S, or

(II) the drug of interest

(a) is not ethacrynic acid, bezafibrate, succinyl-L-tryptophan-L-tryptophan, p-bromobenzyloxyacetic acid, or polyethylene glycol or

(b) is bound through a disulfide to a cysteine residue of the hemoglobin-like protein.

Dwg.0/0

L117 ANSWER 16 OF 16 WPIX (C) 2002 THOMSON DERWENT

AN 1982-09675J [51] WPIX

TI Oxygen carrier for use in blood substitute - comprising haemoglobin covalently bonded to polymer via amide linkage.

DC A96 B04

IN AJISAKA, K; IWASAKI, K; IWASHITA, Y

PA (AJIN) AJINOMOTO KK

CYC 5

PI EP 67029 A 19821215 (198251)* EN 16p <--
R: DE FR GB
JP 57206622 A 19821218 (198305)
US 4412989 A 19831101 (198346)
EP 67029 B 19860430 (198618) EN <--
R: DE FR GB
DE 3270842 G 19860605 (198624)
JP 02006337 B 19900208 (199010)

ADT EP 67029 A EP 1982-302826 19820602; JP 57206622 A JP 1981-89315 19810610

PRAI JP 1981-89315 19810610

REP GB 2055868; No-SR.Pub; US 4136093

IC A61K037-14; C07C103-52; C08G065-32
AB EP 67029 A UPAB: 19930915
An oxygen carrier comprises haemoglobin or its deriv. covalently bonded to a polymer (such as a polyalkylene glycol or polyether) via an amide-bond. The carrier is prepd. by (i) introducing at least one COOH gp. onto the polymer and (ii) reacting the COOH gp. with an amino gp. of the haemoglobin (deriv.).

The oxygen carrier is used in blood substitutes. The carrier is highly safe, e.g. when more than 90% of the blood of rats was exchange transferred with a 6% soln. of the modified haemoglobin, the rats survived, whereas when the rats blood was exchange transferred with 6% bovine serum albumin soln., the rats died before the exchange ratio reached 82%. The modified haemoglobin has LD5 over 4.5 g/kg.
FS CPI
FA AB
MC CPI: A10-E17; A12-V02; A12-V03B; B04-B04D; B04-C03C; B12-H06
ABEQ EP 67029 B UPAB: 19930915
An oxygen carrier comprising haemoglobin or a haemoglobin derivative covalently bonded to a polymer selected from polyethylene glycol, polypropylene glycol, a copolymer of ethylene oxide and propylene oxide, or such a polymer in which at least one hydroxyl group thereof is (a) etherified by an alcohol having from 1 to 16 carbon atoms, (b) esterified by a carboxylic acid having from 2 to 18 carbon atoms, or (c) aminated by an amine having from 1 to 18 carbon atoms, characterised in that the haemoglobin or haemoglobin derivative is covalently bonded to said polymer via an amide bond.

=> d his

(FILE 'HOME' ENTERED AT 15:37:39 ON 28 AUG 2002)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 15:37:49 ON 28 AUG 2002
E HEMOGLOBIN/CN
E HEMOGLOBIN
L1 2888 S E3,E6,E7

FILE 'HCAPLUS' ENTERED AT 15:38:37 ON 28 AUG 2002
E ADAMSON J/AU
L2 36 S E3,E6,E7
L3 2 S E17
E MCINTOSH G/AU
L4 15 S E3
L5 1 S E24
E MC INTOSH G/AU
L6 53 S L2-L5
L7 93373 S HEMOGLOBIN OR HEMOPROTEIN
L8 7 S L6 AND L7
E HEMOSOL/PA,CS
L9 32 S E3-E14
L10 23 S L7 AND L9
E HEMOGLOBIN/CT
E E3+ALL
L11 2644 S E1
E E2+ALL
L12 39033 S E4,E3+NT
E HEMOGLOBIN/CW
L13 36770 S E3,E4
E HEMOPROTEIN/CT
E E4+ALL
L14 2460 S E2
E HEMOPROTEIN/CW

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L15        2460 S E4
L16          23 S L6,L9 AND L11-L15
L17          26 S L8,L10,L16
L18        8933 S L1
L19           4 S L6 AND L18
L20          26 S L17,L19
L21           2 S L20 AND ANTIOXID?
L22           2 S L21 AND CONJUGAT?
L23           1 S L22 NOT HAPTOGLOBIN
L24          25 S L20 NOT L23
                SEL RN L23

     FILE 'REGISTRY' ENTERED AT 15:58:00 ON 28 AUG 2002
L25          18 S E1-E18
L26             STR
L27          50 S L26
L28             STR L26
L29          50 S L28
L30       34574 S L28 FUL
L31           3 S L25 AND L30
L32             STR L26
L33           3 S L32 CSS SAM SUB=L30
L34          68 S L32 CSS FUL SUB=L30
                SAV TEMP L34 KWON926/A
L35          27 S C14H18O4 AND L34
L36          25 S L35 AND 2 5 7 8
L37          25 S L36 AND TETRAMETHYL
L38          12 S L37 NOT (MXS/CI OR COMPD)
L39           8 S L38 NOT (14C# OR 13C# OR ION)
L40             STR L32
L41          50 S L40 CSS SAM SUB=L30
L42         865 S L40 CSS FUL SUB=L30
                SAV TEMP L42 KWON926A/A
L43         696 S L42 AND 1/NC
L44          20 S L43 AND IDS/CI
L45          16 S L44 NOT N/ELS
L46          13 S L45 NOT OC4/ES
L47          11 S L46 NOT PROPANETRICARBOXYLIC
L48          10 S L47 NOT C29H50O4
L49           5 S 36118-45-3 OR 120-72-9 OR 120-73-0 OR 50-81-7 OR 56631-56-2

     FILE 'HCAPLUS' ENTERED AT 16:33:37 ON 28 AUG 2002
L50         783 S L39
L51          11 S L47
L52       13756 S L43
L53       57334 S L49
L54        1207 S TROLOX
                E ANTIOXIDANT/CT
                E E11+ALL
L55       44113 S E5
                E PHENOL/CT
                E PHENOLIC/CT
                E PHENOLS/CT
                E E3+ALL
L56       39759 S E7
L57      495459 S E7+NT
                E PYRAZOLINE
L58        5176 S E3
                E CAROTENOID
L59       24640 S E3
                E CAROTENE/CT
                E E4+ALL
L60       27122 S E8,E9,E7+NT
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                E E40+ALL
L61         30196 S E8+NT
                E RETINOID
L62         10616 S E3
                E QUINONE
L63         37568 S E3
L64         47410 S INDOLE
L65         35719 S PURINE
L66         90913 S ASCORBIC ACID OR VITAMIN(S)C
                E STEROID/CT
                E E70+ALL
L67         51921 S E2
                E ALKALOID/CT
                E E21+ALL
L68         33176 S E2
L69        121979 S E2+NT
L70        212261 S STEROID OR ALKALOID
L71          5491 S L50-L70 AND L7,L11-L15,L18
L72           191 S L71 AND ?CONJUGAT?
L73            15 S L72 AND 63/SC

     FILE 'REGISTRY' ENTERED AT 16:41:25 ON 28 AUG 2002
L74             6 S 111-30-8 OR 578-19-8 OR 512-69-6 OR 1892-57-5 OR 151-51-9 OR

     FILE 'HCAPLUS' ENTERED AT 16:44:18 ON 28 AUG 2002
L75            88 S L74 AND L71
L76            30 S L75 AND L72
L77             4 S L73 AND L76
                  SEL DN AN 1 2
L78             2 S E1-E6
L79            37 S L73,L76 NOT L77
                  SEL DN AN 6 12 28
L80             3 S L79 AND E7-E15
L81             3 S L6,L9 AND L50-L70
L82             2 S L81 NOT HIV
L83            24 S L75 AND 63/SC
L84            24 S L73,L83 NOT L79
L85            22 S L84 NOT L78,L80,L82
                  SEL DN AN 4 22
L86             2 S L85 AND E16-E21
L87             4 S L82,L86
L88          1066 S L50-L54 AND L71
L89            63 S L88 AND 63/SC
L90             3 S L89 AND ?CONJUGAT?
L91            60 S L89 NOT L90
                  SEL DN AN 1
L92             1 S L91 AND E22-E24
L93             4 S L87,L92 AND L2-L24,L50-L73,L75-L92

     FILE 'REGISTRY' ENTERED AT 17:02:48 ON 28 AUG 2002
L94             1 S RAFFINOSE/CN

     FILE 'HCAPLUS' ENTERED AT 17:03:00 ON 28 AUG 2002
L95          7486 S L94 OR RAFFINOSE
L96            69 S L95 AND L7,L11-L15,L18
L97             6 S L96 AND L50-L70
L98             2 S L97 AND 63/SC
L99             4 S L93,L98
L100           11 S L96 AND ?CONJUGAT?
L101            9 S L100 NOT L99
L102            2 S L99 AND L100
L103            4 S L99,L102
                  SEL HIT RN
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     FILE 'REGISTRY' ENTERED AT 17:06:38 ON 28 AUG 2002
L104         15 S E25-E39

     FILE 'HCAPLUS' ENTERED AT 17:07:00 ON 28 AUG 2002
L105          4 S L23,L103
L106          4 S L105 AND L2-L24,L50-L73,L75-L93,L95-L103

     FILE 'REGISTRY' ENTERED AT 17:08:05 ON 28 AUG 2002
L107          1 S 41903-66-6

     FILE 'HCAPLUS' ENTERED AT 17:08:11 ON 28 AUG 2002
L108          1 S L107 AND L7,L11-L15,L18
L109          4 S L106,L108

     FILE 'HCAPLUS' ENTERED AT 17:08:57 ON 28 AUG 2002

     FILE 'REGISTRY' ENTERED AT 17:09:16 ON 28 AUG 2002

     FILE 'WPIX' ENTERED AT 17:10:51 ON 28 AUG 2002
                E WO200056367/PN
L110          1 S E3
L111          1 S EP67029/PN
L112          1 S RU2162707/PN
L113          1 S WO9956723/PN
L114          4 S L110-L113
L115        212 S (A61K038-42 OR C07K014-805)/IC,ICM,ICS
L116         14 S L115 AND A61K047-48/IC,ICM,ICS
L117         16 S L114,L116

     FILE 'WPIX' ENTERED AT 17:17:48 ON 28 AUG 2002
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